UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
Norfolk Division

PFIZER INC., PFIZER LIMITED PFIZER IRELAND PHARMACEUTICALS, (a Partnership), and PFIZER IRELAND PHARMACEUTICALS (an Unlimited Liability Company),	
Plaintiffs and Counterclaim Defendants,	Civil Action No. 2:10-cv-00128-RBS-FBS
v.	
TEVA PHARMACEUTICALS USA, INC.,	
Defendant and Counterclaim Plaintiff.	

TEVA'S POST-TRIAL FINDINGS OF FACT

AND CONCLUSIONS OF LAW ON STANDING AND VALIDITY

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

OTHER AUTHORITIES

INTRODUCTION

Defendant Teva Pharmaceuticals USA, Inc. ("Teva") hereby submits its Post-Trial Findings of Fact and Conclusions of Law on Standing and Validity. Should the Court determine that any conclusion of law is more properly considered an issue of fact, Teva incorporates such issues by reference into its post-trial findings of fact. Should the Court determine that any finding of fact is more properly considered an issue of law, Teva incorporates such issues by reference into its post-trial conclusions of law.

To the extent that Pfizer attempts to introduce different or additional facts and/or legal arguments that were not introduced at trial, Teva reserves the right to object to and/or contest those facts and/or legal arguments, to present any and all rebuttal evidence in response to those facts and/or legal arguments, and/or to present new legal arguments in response to those facts and/or legal arguments.

FINDINGS OF FACT

I. BACKGROUND

A. The Parties In This Case

1. The Plaintiffs and Counterclaim Defendants in this case are Pfizer Inc., Pfizer Limited, Pfizer Ireland Pharmaceuticals (a partnership) and Pfizer Ireland Pharmaceuticals (an unlimited liability company) (collectively, "Pfizer").[1] D.I. 407 (Amended Complaint).

2. Pfizer Inc. is a corporation organized under the laws of the State of Delaware and has its principal place of business located at 235 East 42nd Street, New York, New York. SUF ¶ 1.[2]

3. Pfizer Limited is a corporation organized under the laws of England and has its principal place of business at Ramsgate Road, Sandwich, Kent, England. SUF ¶ 2.

4. Pfizer Ireland Pharmaceuticals ("PIP Pship") is a partnership existing pursuant to the laws of Ireland and has its registered office at Pottery Road, Dun Laoghaire, County Dublin, Republic of Ireland. D.I. 407 at ¶ 4 (Amended Complaint).

5. Pfizer Ireland Pharmaceuticals ("PIP Co.") is a private unlimited liability company incorporated in Ireland having its registered office at Operations Support Group, Ringaskiddy, Co Cork, Ireland. D.I. 407 at ¶ 5 (Amended Complaint).

6. The Defendant and Counterclaim Plaintiff in this case is Teva Pharmaceuticals USA, Inc. ("Teva"). Teva is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454. SUF ¶ 4.

---

[1] Teva contests the standing of each Pfizer entity.

[2] "SUF" refers to the identified paragraph of the Stipulations of Undisputed Facts set forth in the Final Pretrial Order. D.I. 276 at ¶¶ 3-6.

B. **The Dispute**

1. **Pfizer's Sildenafil Citrate New Drug Application**

7. On March 27, 1998, Pfizer received approval from the United States Food and Drug Administration ("FDA") to market a drug product having the active pharmaceutical ingredient sildenafil citrate for the treatment of erectile dysfunction ("ED"). *See* SUF ¶ 15. Pfizer sells that sildenafil citrate drug product in the form of 25 mg, 50 mg and 100 mg tablets under the brand name VIAGRA®. *See* SUF ¶ 15.

8. The FDA approved prescribing information for VIAGRA® states that VIAGRA® is indicated for the treatment of ED by oral administration, taken, as needed, 4 hours to 0.5 hours before sexual activity, with a maximum recommended dosing frequency of once per day. DX 2037 at 24 (Viagra Prescribing Information).

9. The FDA maintains a published list titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly known as the "Orange Book"). *See* SUF ¶ 16. The Orange Book includes, for each FDA approved product, a list of patents identified by the new drug applicant that claim the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

10. The Orange Book lists two patents in connection with VIAGRA®: (1) U.S. Patent No. 5,250,534 ("the '534 patent"), which claims, *inter alia*, the compound sildenafil and pharmaceutically acceptable salts thereof, such as sildenafil citrate (*see* DX 2004 at 20:52-21:7 ('534 patent); SUF ¶ 17), and (2) U.S. Patent No. 6,469,012 ("the '012 patent"), which claims, *inter alia*, a method of using recited compounds, including sildenafil, for the treatment of ED in male animals, including male humans (*see* DX 2001 at 10:1-33 ('012 patent); SUF ¶ 16).

2. **Teva's Proposed Sildenafil Citrate Drug Product**

11. On October 25, 2004, Teva filed Abbreviated New Drug Application ("ANDA") No. 77-342 with the Food and Drug Administration ("FDA") seeking approval to market a 100 mg generic equivalent of VIAGRA® ("Teva's Proposed Sildenafil Citrate Tablets"). PTX 238 (October 2004 ANDA Letter). Teva amended ANDA No. 77-342 on November 19, 2004 to include 25 mg and 50 mg strengths. PTX 0241 (November 2004 ANDA Letter).

12. With its ANDA, Teva submitted a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(III) ("Paragraph III certification") indicating that Teva would not market its product prior to the expiration of the '534 patent. SUF ¶ 20; PTX 244 (Paragraph III Certification). The Orange Book indicates that the term of the '534 patent expires on March 27, 2012. SUF ¶¶ 17-18.

13. Teva also submitted with its ANDA a certification under 21 U.S.C. § 3550)(2)(A)(vii)(IV) ("Paragraph IV certification") asserting that the claims of the '012 patent are invalid or will not be infringed by the commercial manufacture, use or sale of Teva's Proposed Sildenafil Citrate Tablets prior to the expiration of the '012 patent. PTX 244 (Paragraph III Certification); *see* SUF ¶ 19.

14. On December 17, 2004, Teva sent a letter to Pfizer enclosing a detailed statement of the factual and legal bases of Teva's opinion regarding the invalidity, unenforceability or non-infringement of the claims of the '012 patent. PTX 236 (December 2004 Letter); SUF ¶¶ 19, 21.

15. On April 24, 2007, FDA granted Teva tentative approval to market its Proposed Sildenafil Citrate Products. SUF ¶ 22. That approval does not allow marketing of Teva's Proposed Sildenafil Citrate Products because, based on Teva's Paragraph III Certification, Teva cannot market those products until the expiration of the '534 patent. PTX 244 (Paragraph III Certification).

3. **Pfizer's Complaint In This Action**

16. On March 24, 2010, Pfizer sued Teva alleging that the filing of ANDA No. 77-342 with a Paragraph IV certification regarding the '012 patent constituted an act of infringement, and alleging that Teva's manufacture, use or sale of Teva's Proposed Sildenafil Citrate Products would infringe one or more claims of the '012 patent. SUF ¶ 10.

C. **The Patent-In-Suit: The '012 Patent**

17. The '012 patent, titled "Pyrazolopyrimidinones for the Treatment of Impotence," issued on October 22, 2002 from U.S. Patent Application Serial No. 08/549,792 ("the '792 application"). DX 2001 ('012 patent); SUF ¶ 5. The '792 application was filed on March 4, 1996 as a U.S. national stage of International Application No. PCT/EP94/01580 ("PCT '580"), which was filed on May 13, 1994. DX 2001 ('012 patent). The '012 patent claims the benefit of the filing date of British Patent Application No. 9311920.4 ("GB '920"), which was filed on June 9, 1993. DX 2001 ('012 patent). The '012 patent names Peter Ellis and Nicholas Kenneth Terrett as co-inventors. DX 2001 ('012 patent); SUF ¶ 6.

18. The '012 patent issued with 26 claims directed to the administration of prior art compounds for the treatment of ED in male animals. DX 2001 at 6:43-10:39 ('012 patent).

19. Claims 1-19 and 21-23 are directed to the treatment of ED in male animals. DX 2001 at 6:43–9:26, 9:29-35 ('012 patent).

20. Claims 20, 25 and 26 are directed to the treatment of ED in male humans. DX 2001 at 6:42-10:38 ('012 patent).

21. Pfizer gave Teva a covenant not to sue or otherwise hold Teva, its parents, subsidiaries and/or affiliated companies liable for direct or indirect infringement of claims 1-23 of the '012 patent. SUF ¶ 13.

22. Pfizer cancelled claim 24 of the '012 patent during reexamination of the '012 patent. SUF ¶ 7.

23. Pfizer asserts that Teva infringes claims 25 and 26 of the '012 patent. Those are the only claims that Pfizer is asserting in this case. SUF ¶ 11.

24. Claim 25 of the '012 patent claims a method of treating ED in male humans by orally administering an effective amount of any of nine specific prior art compounds recited for use in that method. Claim 25 is reproduced below:

> **25**. A method of treating erectile dysfunction in a male human, comprising orally administering to a male human in need of such treatment an effective amount of a compound selected from:
> 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
> 5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
> 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one;
> 5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one;
> 5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinyl-sulphonyl] phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one;
> 5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
> 5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
> 5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one; and
> 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
> or a pharmaceutically acceptable salt thereof;
> or a pharmaceutical composition containing either entity.

DX 2001 at 10:1-33 ('012 patent).

25. Claim 26 of the '012 patent depends from claim 25 and claims a method of treating ED in male humans by orally administering an effective amount of the following prior art compound, known as sildenafil: 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one. Claim 26 is reproduced below:

> **26**. A method as defined in claim **25**, wherein said compound is 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

DX 2001 at 10:33-39 ('012 patent).

II. PFIZER HAS NOT ESTABLISHED STANDING FOR ANY OF THE NAMED PLAINTIFFS

26. On August 9, 1993, Pfizer Inc. and Pfizer Limited entered into an agreement with Pfizer Corporation and Pfizer Research and Development Company titled "Patent Filing Agreement." PTX-0322 (August 1993 Agreement).

27. The August 9, 1993 Patent Filing Agreement provides that with respect to patent applications filed under the agreement, "Pfizer[, Inc.] will act as agent for Limited, so that such applications and any patent issued thereon shall be held by Pfizer[, Inc.] in trust for Limited, as the beneficial owner thereof." PTX-0322 at 9 (Clause 2.1.2) (August 1993 Agreement).

28. The August 9, 1993 Patent Filing Agreement provides that "the respective rights of the parties hereto [shall be] determined in accordance with the laws of England." PTX-0322 (August 1993 Agreement); Trial Tr. 79:11-15 (Benson).

29. The August 9, 1993 Patent Filing Agreement does not define the term "beneficial owner." PTX-0322 (August 1993 Agreement). No evidenced was adduced at trial regarding the

meaning of the term "beneficial owner" in accordance with the laws of England. Trial Tr. 77:14-22 (Benson).

30. The August 9, 1993 Patent Filing Agreement states that "[i]n consideration of Pfizer [Inc.] undertaking the obligations referred to in clause 2 hereof with respect to Limited Property patent applications, Pfizer [Inc.] shall be entitled to obtain a non-exclusive license from Limited with respect to any such Limited Property in the USA …." PTX 0322 at 6 (Clause 3.1) (August 1993 Agreement).

31. Pfizer provided no evidence at trial in support of a contention that the August 9, 1993 Patent Filing Agreement has effect with respect to the '012 patent and conveys to Pfizer Limited any interest in the '012 patent.

32. Drs. Peter Ellis and Nicholas Kenneth Terrett are the sole inventors listed on the face of the '012 patent. PTX 0001 at 1 ('012 patent).

33. On October 10, 1995, Drs. Ellis and Terrett signed a document titled "Assignment" that purports to assign the "entire right, title and interest" in the patent application that issued as the '012 patent and the inventions disclosed in that patent application to Pfizer Inc.. PTX 0363 (October 1995 Assignment); Trial Tr. 81:7-82:13 (Benson).

34. On October 10, 1995, Pfizer Limited executed a Consent Of Pfizer Limited, which states that "by virtue of the terms of employment with Pfizer Limited … Pfizer Limited is entitled to an assignment of the entire right, title and interest in and to all inventions, whether joint or sole, made by [Dr.] Ellis and [Dr.] Terrett and whereas Pfizer Limited desires that Pfizer Inc. receive the full benefits of the foregoing assignment by its aforesaid employee(s), Pfizer Limited … hereby consents to the foregoing assignment by its aforesaid employee(s)". PTX 0363 (October 1995 Assignment); Trial Tr. 68:3-15, 82:4-83:7 (Benson).

35. On February 27, 1996, Drs. Ellis and Terrett signed a document titled "Assignment" that purports to assign "entire right, title and interest" to the application that issued as the '012 patent and the inventions disclosed in that application to Pfizer Inc. PTX-0323 (February 1996 Assignment).

36. On February 27, 1996, Pfizer Limited executed a Consent Of Pfizer Limited, which states that "by virtue of the terms of employment with Pfizer Limited … Pfizer Limited is entitled to an assignment of the entire right, title and interest in and to all inventions, whether joint or sole, made by [Dr.] Ellis and [Dr.] Terrett and whereas Pfizer Limited desires that Pfizer Inc. receive the full benefits of the foregoing assignment by its aforesaid employee(s), Pfizer Limited … hereby consents to the foregoing assignment by its aforesaid employee(s)". PTX 0863 (February 1997 Consent).

37. The February 27, 1996 assignment did not operate as a valid assignment of any right, title or interest to the application that issued as the '012 patent and the inventions disclosed in that application to Pfizer Inc. Trial Tr. 70:6-14 (Benson).

38. In a January 1, 1997 License Agreement – "Subject Matter: Sildenafil", Pfizer Limited purported to grant to Pfizer Pharmaceuticals Production Corporation ("PPPC"), "a company organized under the laws of the Republic of Panama," "an exclusive license under U.S. Patent Rights to make, use, sell, and offer for sale Licensed Product in the United States." PTX-0324 at 4 (January 1, 1997 Agreement); Trial Tr. at 89:17–22 (Benson). "U.S. Patent Rights" is defined in the License Agreement to mean several patents and patent applications including the application that issued as the '012 patent. PTX 0324 at 4 (January 1, 1997 Agreement). "Licensed Product means any drug intended for human use containing compound". PTX 0324 at 4 (January 1, 1997 Agreement). "'Compound' means sildenafil …. together with the citrate salt

and any other salts thereof." PTX 0324 at 4 (January 1, 1997 Agreement). When asked "how could you possible know that those [beneficial] rights were sufficient to grant the exclusive license that [the January 1, 1997 License Agreement] purports to grant?", Pfizer's Mr. Benson testified: "I don't know that they could do that." Trial Tr. 88:4-10 (Benson).

39. The January 1, 1997 License Agreement purported to grant PPPC to "make, use, sell, and offer for sale" one product—a product containing sildenafil—in the United States. PTX 0324 at 2, 3, 4 (January 1, 1997 Agreement); Trial Tr. 89:17–22 (Benson).

40. The January 1, 1997 License Agreement (PTX-0324) that was purportedly transferred to PIP Co. is *not* an exclusive license to the '012 patent. PTX 0324 (January 1, 1997 Agreement); Trial Tr. 89:17–90:17 (Benson).

41. The January 1, 1997 License did not grant any rights of enforcement with respect to the '012 patent or the application that resulted in the '012 patent. PTX 0324 at 4 (January 1, 1997 Agreement).

42. In the January 1, 1997 License Agreement, Pfizer Limited retained a Conversion Right, Maintenance of Patents and Prosecution of Applications, a right to receive Running Royalties and a right of Termination for Default if the royalties are not paid in accordance with the agreement. PTX 0324 (January 1, 1997 Agreement). The Conversion Rights of the January 1, 1997 License Agreement allows Pfizer Limited "to convert" "on the Conversion Date applicable to said patent or any time thereafter" the exclusive license granted to the licensee, and any sublicense, "into a non-exclusive license for the remaining term of said patent" and states Pfizer Limited "shall have the right to grant such further non-exclusive licenses" to others. PTX 0324 at 4 (Clause II.D) (January 1, 1997 Agreement). The Conversion Date of the January 1,

1997 License Agreement as it pertains to the manufacture and sale of sildenafil has passed. PTX 0324 at 2 (January 1, 1997 Agreement).

43. The Maintenance of Patents and Prosecution of Applications provision of the January 1, 1997 License Agreement requires Pfizer Limited and Pfizer Inc. to maintain "all patents comprising the Patent Rights", "pay or have paid . . . all dues, taxes, charges and annuities for the maintenance of such Patent Rights," and "prosecution or have prosecuted by Pfizer Inc. all patent applications included in the Patent Rights." PTX 0324 at 7-8 (Clause IV.A) (January 1, 1997 Agreement). The Running Royalties provision of that agreement requires PIP Co. to pay Pfizer Limited a substantial royalty, from 18% to 23% on net sales, until the late patent expires under the agreement. PTX 0324 at 6 (Clause III.B) (January 1, 1997 Agreement).

44. On January 15, 1998, PPPC and Pfizer Pharmaceuticals Production Company Limited ("PPPCL"), "a private limited company incorporated in the Isle of Man," entered into a "Sale Agreement of the Entire Irish Business and Irish Assets" in which PPPC sold "its entire Irish business and assets" to PPPCL including PPPC's rights under the January 1, 1997 License Agreement. PTX 0325 at 4, 9-10 (January 1998 Agreement); Trial Tr. 71:21–72:6, 91:3-91:19 (Benson).

45. On November 14, 2000, PPPCL entered into an Agreement For Sale of Business and Assets, in which it sold its business to an entity called Pfizer Ireland Pharmaceuticals ("PIP") that, although it had the same name, is a separate entity from PIP Pship and PIP Co. including PPPCL's rights under the January 1, 1997 License Agreement. PTX 0326 at 10 (November 2000 Agreement); Trial Tr. 72:10–21, 93:20-94:17 (Benson).

46. On November 28, 2003, PIP, Pfizer Manufacturing LLC ("PM LLC") and Pfizer Production LLC ("PP LLC") entered into an Agreement for Sale of Business and Assets, in

which Pfizer Ireland Pharmaceuticals sold its business, including its rights under the January 1, 1997 Licensing Agreement, to a partnership comprised of Pfizer Ireland Pharmaceuticals, PM LLC and PP LLC, which is PIP Pship. PTX 0209 at 1-3, 5 (November 2003 Agreement); Trial Tr. 73:4-15, 94:18-95:9 (Benson). On January 10, 2011, PIP Pship and PIP Co. entered into an Agreement for Sale of Business and Assets in which PIP Pship sold its business, including PIP Pship's rights under the January 1, 1997 License Agreement, to PIP Co. PTX 0210 at 7 (January 2011 Agreement); Trial Tr. 73:20-74:10, 95:15-97:9 (Benson).

III. THE EXPERTS

A. Teva's Experts

1. Dr. Jackie D. Corbin

47. The Court qualified Teva's expert, Dr. Jackie Corbin, as an expert in the fields of pharmacology, physiology, and enzymology, including cyclic nucleotides, phosphodiesterases, phosphodiesterase inhibitors and uses thereof. Trial Tr. 115:25-116:8 (Corbin).

48. Dr. Corbin testified about the anatomy of the penis, the mechanism of erection and the different molecules involved in the pharmacological pathway that controls the penile erection. Dr. Corbin also testified about the prior art and what it would have taught a person of ordinary skill in the art, and his opinion that claims 25 and 26 of the '012 patent are obvious in view of the prior art. Dr. Corbin also testified about his opinion that claims 25 and 26 of the '012 patent are invalid for obviousness type double patenting.

2. Dr. Culley C. Carson, III

49. The Court qualified Teva's expert, Dr. Culley Carson, as an expert in urological medicine and the treatment of erectile dysfunction. Trial Tr. 200:7-13 (Carson).

50. Dr. Carson testified regarding the knowledge of a POSA in the 1993-94 timeframe about the anatomy and physiology of the penis, the mechanism of penile erection,

erectile dysfunction, treatment of erectile dysfunction and other relevant concepts and terminology, and provided to the Court his opinions that a POSA in May 1994 would have been motivated to orally administer sildenafil to treat ED and would have had a reasonable expectation that oral administration of sildenafil would effectively treat ED. Trial Tr. 200:20-201:6 (Carson).

3. **Dr. Jerry Hausman**

51. The Court qualified Teva's expert, Professor Jerry Hausman, as an expert in economics generally and in the field of applied economics in particular. Trial Tr. 599:15-19 (Hausman).

52. Professor Hausman testified about whether there is a nexus between the sales and profits of Viagra® and claims 25 and 26 of the '012 patent. Trial Tr. 599:21-25 (Hausman).

4. **Dr. Cameron K. Weiffenbach**

53. The Court qualified Teva's expert, Cameron Weiffenbach, as an expert in United States Patent and Trademark Office ("USPTO") practice and procedure. Trial Tr. 1101:15-22 (Weiffenbach).

54. Mr. Weiffenbach testified regarding the process and procedure for prosecuting and examining patent applications in the USPTO, patent reexamination proceedings and reissue applications. Mr. Weiffenbach also testified regarding the USPTO practice, rules and procedures relating to the duty of candor and good faith owed to the USPTO by persons substantively involved in the prosecution of a patent, and the duty to disclose information about foreign litigation involving the same subject matter as the subject matter of the claims involved in the prosecution of an application pending before the USPTO. Trial Tr. 1102:14-1103:5 (Weiffenbach).

B. **Pfizer's Experts**

1. **Dr. Peter Ellis**

55. Dr. Ellis testified as an expert for Pfizer in the field of pharmacology, with knowledge of the biological mechanisms of the erectile process and of erectile dysfunction and the treatment of erectile dysfunction, PDEs and PDE inhibitors. Trial Tr. 666:1-9 (Ellis).

56. Dr. Ellis did not provide any definition of the person of ordinary skill in the art regarding whom he testified. *See* Trial Tr. 657-794 (Ellis).

57. Dr. Ellis is not a medical doctor or a urologist. Trial Tr. 761:1-6 (Ellis).

58. Dr. Ellis is the Director and only employee of Pentropy Consulting Limited ("Pentropy"). Trial Tr. 761:7-12.

59. Pentropy was formed in October 2009, and since that time all of Pentropy's revenues have come from work for Pfizer, including work on litigation involving Dr. Ellis' '012 patent. Trial Tr. 761:13-25 (Ellis).

60. Dr. Ellis is one of the named inventors on the face of the '012 patent. DX 2001 ('012 Patent).

2. **Dr. Nicholas Terrett**

61. Dr. Terrett testified as an expert for Pfizer in medicinal chemistry. Trial Tr. 974:11-17 (Ellis).

62. Dr. Terrett did not provide any definition of the person of ordinary skill in the art regarding whom he testified. *See* Trial Tr. 968-1011 (Terrett).

63. Dr. Terrett is one of the named inventors on the face of the '012 patent. DX 2001 ('012 Patent).

3. **Dr. Irwin Goldstein**

64. Dr. Goldstein testified as an expert for Pfizer in urology and sexual medicine. Trial Tr. 890:22-891:13 (Goldstein).

65. Dr. Goldstein has consulted for Pfizer since 1994 and was heavily involved with the development of sildenafil as a therapeutic drug, and continued to work with Pfizer to educate physicians about Viagra and ED. Trial Tr. 939:15-940:17.

4. **Dr. Louis Ignarro**

66. Dr. Ignarro is neither a medical doctor nor an expert in urology. Trial Tr. 839:7-12, 854:17-22 (Ignarro).

67. Dr. Ignarro did not provide any definition of the person of ordinary skill in the art regarding whom he testified. *See* Trial Tr. 801-885 (Ignarro).

68. Dr. Ignarro never focused on the development of cyclic GMP PDE inhibitors. Trial Tr. 839:19-23 (Ignarro).

69. Dr. Ignarro's focus was and remains on the properties and potential benefits of Nitric Oxide. PTX 004 at PFZFH0003188-3249 at 3216 at 404:3-10 (Transcript of *Lilly v. Pfizer* in the UK), PFZFH0003814-3857 at 3853-3855 at ¶¶ 144-149 (UK Decision regarding UK counterpart of '012 patent); Trial Tr. 837:12-884:24 (Ignarro).

70. Dr. Ignarro's laboratory confirmed that the first messenger was nitric oxide, and that the second messenger was cyclic GMP for relaxation of smooth muscle in human penile tissue. Trial Tr. 848:12-849:13 (Ignarro).

71. In 1993, Dr. Ignarro did not believe that a specific cyclic GMP inhibitor could be used for the treatment of erectile dysfunction in humans even though a Ph.D. student in his laboratory, Dr. Bush, specifically made that recommendation. DX 2165 (Bush Dissertation); Tr. 838:12-19, 855:8-856:4, 861:21-862:14, 865:24-866:18, 867:12-869:8, 870:10-18 (Ignarro).

72. Dr. Ignarro was so fixated on the front end of the L-arginine – Nitric Oxide – cyclic GMP pathway that he discounted findings that demonstrated the role that cyclic GMP PDE inhibitors played on the back end of the L-arginine – Nitric Oxide – cyclic GMP pathway. PTX 004 at PFZFH0003188-3249 at 3216 at 404:3-10 (Transcript of *Lilly v. Pfizer* in the UK), PFZFH0003814-3857 at 3853-3855 at ¶¶ 144-149 (UK Decision regarding UK counterpart of '012 patent); DX 2165 (Bush Dissertation); Tr. 838:12-19, 855:8-856:4, 861:21-862:14, 865:24-866:18, 867:12-869:8, 870:10-18, 878:6-10, 882:17-884:12 (Ignarro).

73. By June 9, 1993, a POSA would have understood the L-arginine – Nitric Oxide – cyclic GMP pathway to disclose a first and second messenger. A POSA would not have focused on the first messenger (i.e., nitric oxide) to the exclusion of the second messenger (*i.e.*, cyclic GMP PDE inhibitors), when considering potential treatments of erectile dysfunction in humans. PTX 004 at PFZFH0003188-3249 at 3216 at 404:3-10 (Transcript of *Lilly v. Pfizer* in the UK), PFZFH0003814-3857 at 3853-3855 at ¶¶ 144-149 (UK Decision regarding UK counterpart of '012 patent).

5. **Dr. Henry Grabowski**

74. Professor Grabowski has served as an expert consultant for Pfizer in three separate litigations. Pfizer funds some of his academic research in pharmaceuticals and health economics, and he is being compensated $750 per hour for his work on this litigation. Trial Tr. 1036:7-1036:20 (Grabowski).

75. Professor Grabowski has testified at trial and in depositions over a dozen times in pharmaceutical patent litigations, and each time he has testified at trial, it has been on behalf of a branded pharmaceutical company. Trial Tr. 1035:19-136:6 (Grabowski).

76. Professor Grabowski agrees that no company could make, use or sell sildenafil without a license from Pfizer under the '534 patent, even if a company utilized the research

exemption to develop sildenafil for treating ED before Pfizer did. Trial Tr. 1033:2-11, 1037:7-13 (Grabowski).

77. Although Professor Grabowski argues that a hypothetical company could have utilized the research exemption to develop sildenafil for the treatment of ED before Pfizer did, he did not offer any real-world examples where a for-profit company developed a new use for a patented compound owned by a second company. He investigated that issue for purposes of this litigation by calling three individuals who work at for-profit pharmaceutical companies, and he could only provide three examples, all of which involve non-profit companies that developed new uses for patented compounds owned by others. Trial Tr. 1041:22-1044:23 (Grabowski).

78. The examples of non-profit companies offered by Professor Grabowski are not instructive because non-profit companies do not demand as high a royalty as for-profit companies. Trial Tr. 633:9-16 (Hausman). Professor Grabowski refused to offer an opinion about whether Pfizer would have a negotiating advantage in such a hypothetical scenario despite that he injected the hypothetical scenario into this litigation. Trial Tr. 140:23-141:3 (Grabowski).

79. Professor Grabowski does not deny that, if another company developed a use of sildenafil for the oral treatment of ED before Pfizer did, Pfizer could avoid negotiating a license with that company by developing a PDE5 inhibitor other than sildenafil for the oral treatment of ED. He does not know how many PDE5 compounds Pfizer had designed, synthesized and tested leading up to the 1993-94 timeframe. Trial 1037:20-1040:22 (Grabowski).

80. Professor Grabowski agrees that, from 2003 to 2010, Pfizer has been unable to prevent the sale of Cialis® and Levitra® with the ‘534 patent or claims 25 and 26 of the ‘012

patent and that Viagra's® market share has steadily declined since Cialis® entered the market in 2003. Trial Tr. 1033:12-1033:22, 1044:24-1045:6 (Grabowski).

81. Professor Grabowski does not deny that if Pfizer had been able to maintain the validity of claim 24 of the '012 patent, which was directed to the oral administration of all PDE5 inhibitors to treat ED, that Pfizer would have been able keep Cialis® and Levitra® off the market and sell more Viagra® than it has been able to sell with Cialis® and Levitra® on the market. Trial Tr. 1033:23-1034:8, 1034:13-1035:1 (Grabowski).

82. Professor Grabowski agrees that the number of Viagra® prescriptions has decreased over time. Although the wholesale dollars of Viagra® have increased or remained flat over time, Professor Grabowski agrees that the price of Viagra® has increased over time, and he failed to explain how a price increase impacts his analysis. Trial Tr. 1032:17-25 (Grabowski).

83. Professor Grabowski did not offer an opinion about whether there is a nexus between the sales and profits of Viagra® and claims 25 and 26 of the '012 patent based on whether those claims are going to keep a generic sildenafil off the market after the '534 patent expires. Trial Tr. 1045:7-18 (Grabowski).

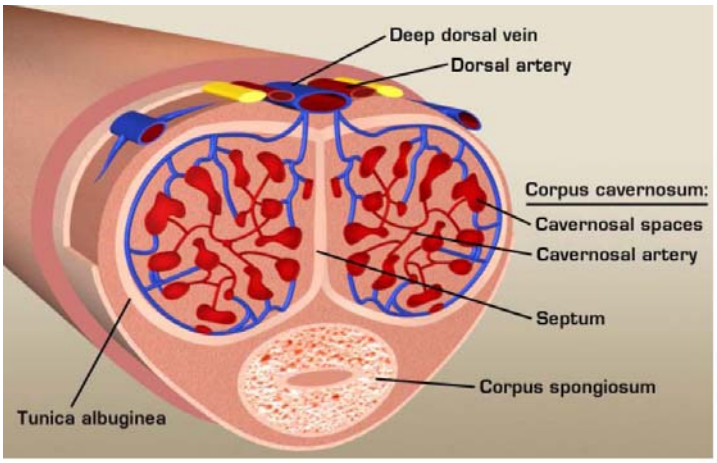
IV. GENERAL OVERVIEW OF THE TECHNOLOGY

A. Erectile Dysfunction

84. The Court has defined erectile dysfunction as "an inability to obtain or sustain an erection adequate for intercourse." D.I. 136 at 15.

B. General Anatomy And Physiology Of The Penis

85. The figure below depicts a cross-section of a human penis: Trial Tr. 118:9–119:24 (Corbin), 201:7–202:25 (Carson).



86. The human penis contains erectile tissue called the corpus cavernosum. Trial Tr. 201:7–202:25 (Carson). The corpus cavernosum consists of two corpora cavernosa that run the length of the penis. Trial Tr. 118: 9-15 (Corbin), 201:7–202:25 (Carson).

87. Cavernosal tissue is sponge-like and composed of a meshwork of interconnected cavernosal spaces, which are lined by vascular endothelium and separated by bundles of smooth muscle. Trial Tr. 201:7–202:25 (Carson). Each of the corpora cavernosa is surrounded by a thick fibrous sheath, the tunica albuginea. Trial Tr. 118:9-23 (Corbin), 201:7–202:25 (Carson). The cavernous bodies share a perforated septum, which allows them to function as a single unit. Trial Tr. 201:7–202:25 (Carson).

88. Arteries supply blood to the human penis. Trial Tr. 201:7-202:25 (Carson). Veins drain blood from the human penis. Trial Tr. 201:7–202:25 (Carson).

89. In a flaccid penis, the effect of sympathetic nerve stimulation, which produces contraction of smooth muscle cells, overrides the effect of parasympathetic nerve stimulation. Trial Tr. 203:15–205:24 (Carson). In erection, the latter nerve effect produces relaxation of the smooth muscle cells, and overrides the sympathetic nerve stimulation. Trial Tr. 203:15–205:24 (Carson). This was known by June 1993. *See, e.g.*, DX 2176A at 1652 (Bush 1992); DX 2170A

at 848-49 (Ignarro 1990); DX 2109A at 90 (Rajfer 1992); DX 2165 at 7, 10–11 (Bush Dissertation); Trial Tr. 204:11–205:24 (Carson).

90. During tumescence, the penis increases in volume due to the accumulation of blood in the cavernous bodies of the corpus cavernosum. Trial Tr. 201:7–202:6, 206:25–207:14 (Carson). Tumescence of the penis causes the penis to become erect. Trial Tr. 206:25–207:14 (Carson). In the erect state, the shaft of the penis feels rigid, and the intracavernous pressure (*i.e.*, blood pressure within the corpus cavernosum) is close to the mean arterial blood pressure. Trial Tr. 206:25–207:14 (Carson). The erectile tissue becomes engorged because the inflow resistance of the cavernous bodies is lower than the outflow resistance. Trial Tr. 201:7–202:25, 206:25–207:14 (Carson).

91. Penile erection is mediated mainly via the pelvic nerves, which cause rapid dilatation of the penile arteries, greatly increasing arterial inflow and rapidly filling the corpora cavernosa. Trial Tr. 203:15–205:24 (Carson). The penis elongates, but initially the intracavernous pressure remains unchanged. In the tumescence phase, the intracavernous pressure increases rapidly causing penile engorgement and erection. Trial Tr. 206:25–207:14 (Carson). In the full erection phase, the relaxed trabecular muscle will expand and, together with the increased blood volume, compress the veins that drain blood from the penis against the tunica albuginea, reducing venous outflow and increasing intracavernous pressure to 10-20 mm Hg below the systolic blood pressure. Trial Tr. 201:7–202:25 (Carson). In the skeletal or rigid erection phase, the intracavernous pressure increases well above the systolic pressure as a consequence of voluntary or reflexogenic contraction of the ischiocavernosus and bulbocavernosus muscles. Trial Tr. 206:25–207:14 (Carson).

92. During detumescence there is a contraction of the cavernous smooth muscles, decrease in arterial blood flow, and full restoration of venous outflow. Trial Tr. 207:15-24 (Carson).

C. **Body Signals (Messengers): cAMP And cGMP**

93. By June 9, 1993, it was well known that for human body parts to function in an organized manner, it is necessary for those body parts to communicate with each other. That communication is accomplished by the passing of signals from one body part to another. Signals that pass from a nerve to a body tissue are called neurotransmitters. Trial Tr. 120:2–22 (Carson).

94. There are three neurotransmission pathways in the human body. In general, adrenergic nerves are mediated by epinephrine and norepinephrine (adrenalin and noradrenalin), cholinergic nerves are mediated by acetylcholine, and, with respect to the penis, non-adrenergic, non-cholinergic nerves ("NANC") are mediated by nitric oxide ("NO"). *See* Trial Tr. 204:11–205:24 (Carson), 719:7-17 (Ellis).

95. Once a signal arrives at a particular target body part, such as the penis, it acts on the cells of that body part to produce effects. Trial Tr. 120:2-22 (Corbin).

96. By June 9, 1993, it was known that in some cases the signal penetrates into the cells to act on a target substance within the cells. Trial Tr. 120:2-22 (Corbin). Such signals are called "first messengers." DX 2073 at 12 (Ellis Deposition Transcript). In other cases, the signal first acts on a receptor at the surface of the cells, and the receptor transmits another signal that acts within the cell to propagate the signal. The signal transmitted by the receptor is called a "second messenger." DX 2059 at 3 (Bell Affidavit); DX 2060 at 1819 (Terrett 1996); DX 2214 at 258 (Carson 1995); DX 2038 at PFZ04277829 (Sildenafil Package Insert); Trial Tr. 848:12-15 (Bush). The entire process from initiation of the first signal to the final effect of that signal at the

end of the pathway is called a signaling cascade. PTX 286 at 13729 (Corbin 1999); PTX 294 at 459 (Francis 2003); DX 2169 at 65-68 (Ignarro 1998).

97. In the late 1950s and early 1960s, two second messengers known as cyclic adenosine monophosphate ("cAMP") and cyclic guanasine monophosphate ("cGMP") were discovered. DX 2040 at 330 (Ashman); DX 2251 at 400-401 (Robison 1971).

98. Cyclic AMP and cyclic GMP are synthesized in cells by enzymes called cyclases. Guanylate cyclase, which is also known as guanylyl cyclase, synthesizes cGMP from guanosine triphosphate ("GTP"). DX 2251 at 404 (Robison 1971); Trial Tr. 120:6-22 (Corbin); Trial Tr. 204:11–205:24 (Carson).

99. In the 1970s, cGMP-dependent protein kinase ("PKG") was discovered. *See* DX 2268A at 506-507 (Francis 1988). Later in the 1970s it was found that cGMP could mediate the effects of signals such as the nitric oxide donor, sodium nitroprusside, on smooth muscle relaxation. DX 2252A at 750 (Schultz 1977).

100. Later studies using cGMP analogs showed that PKG is a cGMP mediator of smooth muscle relaxation. DX 2268A at 516 (Francis 1988).

101. By June 9, 1993, it was known that cGMP causes smooth muscle relaxation. PTX 88 at 185-187 (Ignarro 1985); DX 2249A at 211 (Gruetter 1979); Trial Tr. 133:12–135:14 (Corbin), 204:11–205:24 (Carson). Elevation of cAMP in smooth muscle also was known to produce those effects. PTX 88 at 171-172 (Ignarro 1985).

102. By June 1993, smooth muscle was known to be present in the gastrointestinal tract, pulmonary system, all the blood vessels, and the penile corpus cavernosum, among other tissues. Trial Tr. 206:12-17 (Carson), 314:16–316:4 (Corbin).

D. **Nitric Oxide And Its Role**

103. By 1980, it had been reported that the biochemical pathway that mediates smooth muscle relaxation in vascular tissue is activated by a chemical substance known as endothelium-derived relaxing factor ("EDRF"). Trial Tr. 123:16-124:9 (Corbin); DX 2165 at 15 (Bush Dissertation); DX 2248A at 373 (Furchgott 1980); DX 2461 at 26 (Murad 1994); Terrett Dep. Tr. at 36:05–38:15. *See* DX 2258A at 9265 (Ignarro 1987).

104. In 1987, a team of researchers at UCLA confirmed that EDRF is actually NO. DX 2165 at 16 (Bush Dissertation); DX 2258A at 9265 (Ignarro 1987); Trial Tr. 123:16-124:9 (Corbin), 539:10-17 (Bush).

105. In the 1980s, it was known that EDRF/NO readily permeates vascular smooth muscle cells and, once in the cells, activates guanylate cyclase, (DX 2165 at 15–17, 21–23 (Bush Dissertation); DX 2258A at 9269 (Ignarro 1987); DX 2461 at 25-27 (Murad 1994); PTX 88 at 184 (Ignarro 1985)), and that once activated, guanylate cyclase synthesizes cGMP from GTP (Trial Tr. 121:21-122:7 (Corbin); Terrett Dep. Tr. at 233:10-20).

106. By 1988, it was known that in the human body NO is synthesized from the amino acid L-arginine in vascular endothelial cells. Trial Tr. 124:6-17, 134:1-135:14 (Corbin); DX 2165 at 17–18 (Bush Dissertation); DX 2263A at 664 (Palmer 1988).

107. By 1993, it was known that NO is a neurotransmitter that is secreted from nerve endings and endothelial cells. Trial Tr. 123:16-124:2, 134:1-135:14 (Corbin); DX 2165 at 15–17, 21–23 (Bush Dissertation); DX 2170A at 848-849 (Ignarro 1990).

E. **Cyclic Nucleotide Phosphodiesterases ("PDEs")**

108. By June 9, 1993, it was known that the cyclic nucleotides cAMP and cGMP are degraded in the body by enzymes called cyclic nucleotide phosphodiesterases (PDEs). Trial Tr.

123:7–13, 124:18–22 (Corbin); DX 2257 at 150 (Beavo & Reifsnyder 1990); DX 2454 at 3 (Beavo 1990).

109. Enzymes are proteins in the body that catalyze chemical reactions. In an enzymatic reaction, the enzyme binds a molecule, known as a substrate, and converts that substrate molecule into a different molecule, known as a product. Trial Tr. 121:21-122:7 (Corbin).

110. In the 1993 timeframe it was known that PDEs bind cAMP and cGMP as substrates and break them down into degradation products (5'-AMP or 5'-GMP) that are not active as second messengers in their respective pathways. Trial Tr. 123:7-15, 124:18-126:12 (Corbin); DX 2454 at 3 (Beavo 1990).

111. In the 1993 timeframe, it was believed that the action of PDEs was the main mechanism for eliminating cAMP or cGMP in the body. Trial Tr. 123:7-15, 124:18-126:12 (Corbin); DX 2454 at 3 (Beavo 1990).

112. In the 1993 timeframe, it was understood that PDEs reduce or inhibit the effect of any signaling cascade involving cAMP or cGMP. Trial Tr. 124:18-126:12 (Corbin).

113. In 1993, it was known that some PDEs degrade cAMP, some degrade cGMP, and some degrade both. Trial Tr. 124:18-126:12 (Corbin).

114. In 1990, the known PDEs were classified into five PDE families, or "isozymes": PDE I – PDE V. Trial Tr. 124:23-125:2 (Corbin); DX 2257 at 151 (Beavo & Reifsnyder 1990); DX 2454 at 6–11 (Beavo 1990). Over the next five years, the PDE isozymes PDE I –V were renamed using Arabic numerals as PDE1 – PDE5, respectively. Trial Tr. 124:23-125:14 (Corbin); DX 2256A at 726–727 (Beavo 1995). The table below lists the PDE isozymes and what they degrade:

PDE	Distinguishing Factor	Degrades
PDE1	$Ca2^{+/}$calmodulin-stimulated PDEs	cAMP and cGMP
PDE2	cGMP-stimulated PDEs	cAMP and cGMP*
PDE3	cGMP-inhibited PDEs	cAMP and cGMP**
PDE4	cAMP-specific PDEs	cAMP
PDE5	cGMP-specific PDEs	cGMP

* In body cells, PDE2 was thought to degrade cGMP only at very high concentrations
** In body cells, PDE3 was thought to degrade mainly cAMP

Trial Tr. 124:23-126:5 (Corbin); DX 2257 at 151 (Beavo 1990); DX 2256A at 727-738 (Beavo 1995).

115. PDE5 has been referred to in the art as PDE V_A. Trial Tr. 152:15-153:6 (Corbin).

116. In the 1993 timeframe, cGMP PDE referred to PDE1 and PDE5, and cAMP PDE referred to PDE2, PDE3 and PDE4. Trial Tr. 123:7–13 (Corbin), 208:25-209:6, 274:24-275:10 (Carson), 775:2–10 (Ellis).

F. **PDE Inhibitors**

117. An inhibitor is a molecule that binds an enzyme and decreases or blocks the activity of that enzyme. Trial Tr. 126:13-127:1 (Corbin).

118. Compounds that inhibit the same enzyme may inhibit that enzyme to different degrees. If a compound has a higher potency for inhibition of a particular enzyme, a lower concentration of that compound is necessary to achieve the same level of inhibitory effect as a less potent inhibitor of that enzyme. Trial Tr. 127:2–20 (Corbin).

119. The potency of a particular compound as an inhibitor for a particular substrate is often expressed in terms of half-maximal inhibitory concentration (IC_{50}). The IC_{50} of a compound is the concentration of the compound required to inhibit 50% of the activity of the substrate on which the compound is acting. A lower IC_{50} value therefore corresponds to a more potent compound. Trial Tr. 127:2–25 (Corbin).

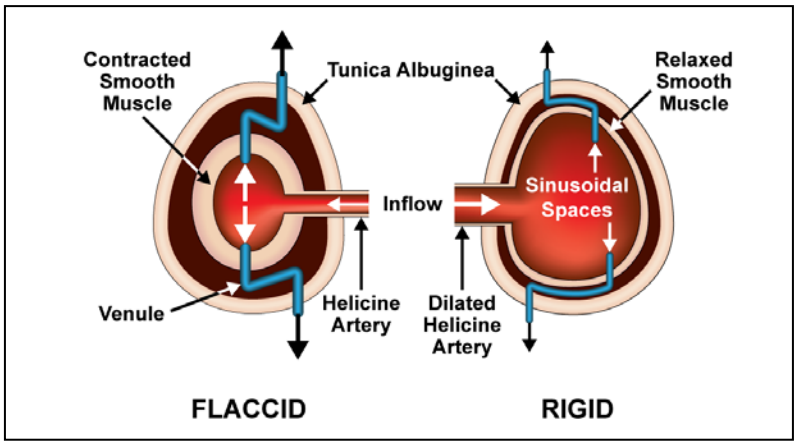
120. PDE inhibitors may have inhibitory activity against more than one PDE isozyme. Trial Tr. 128:1–2 (Corbin). A PDE inhibitor that inhibits multiple PDE isozymes at relatively similar potencies is typically termed a non-selective PDE inhibitor. Trial Tr. 128:3–5 (Corbin). A PDE inhibitor that inhibits one PDE isozyme more potently than other PDE isozymes is referred to as a selective inhibitor of that PDE isozyme. Trial Tr. 128:6–17 (Corbin). The selectivity of an inhibitor for one PDE isozyme over another PDE isozyme is equal to the ratio between the inhibitor's IC_{50} values for the two phosphodiesterases in question. Trial Tr. 128:11–17 (Corbin).

121. There are a number of naturally occurring PDE inhibitors. Trial Tr. 128:18–22 (Corbin). In the 1960s, it was known that caffeine inhibits PDEs by competing with cAMP or cGMP for those enzymes. Trial Tr. 128:18-129:3 (Corbin). That competition takes place because of the partial similarity in the structures of caffeine and cAMP or cGMP. PTX 286 at 13731 (Corbin 1999). Another natural PDE inhibitor, theophylline is structurally similar to caffeine. Theophylline and caffeine are non-selective PDE inhibitors. Trial Tr. 128:18-129:5 (Corbin), 221:7-23 (Carson).

122. By June 1993 it was known that some of the different families of PDEs are selectively inhibited by particular synthetic inhibitors. Trial Tr. 129:6–130:2 (Corbin); DX 2257 at 154 (Beavo & Reifsnyder 1990). For example, vinpocetin selectively inhibited PDE1, EHNA selectively inhibited PDE2, milrinone selectively inhibited PDE3, rolipram selectively inhibited PDE4, and zaprinast selectively inhibited PDE1 and PDE5. Trial Tr. 129:6–130:2 (Corbin), 221:7-23 (Carson); DX 2257 at 154 (Beavo & Reifsnyder 1990). Zaprinast is one to two orders of magnitude more selective for PDE5 than PDE1. Trial Tr. 129:22–130:2 (Corbin); DX 2138A at 152 (Murray 1993); DX 2276A at 14966 (Thomas 1990).

G. **Human Erectile Function / Mechanism Of Erection**

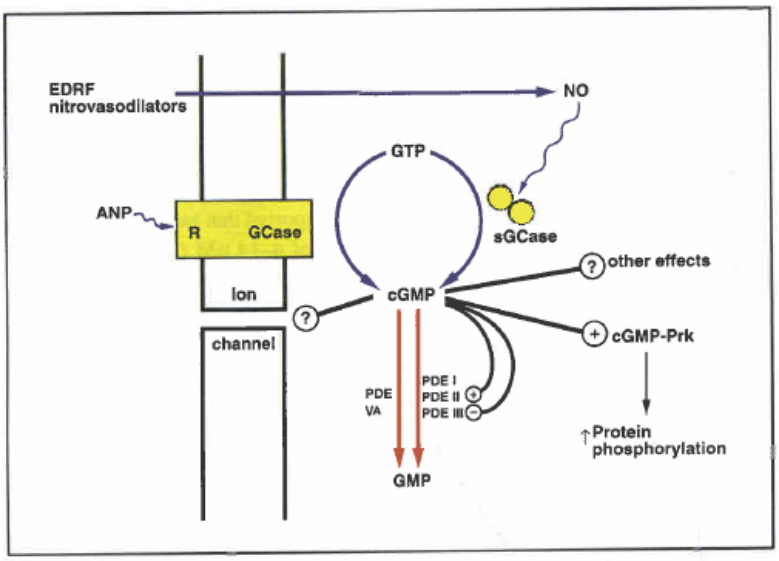
123. The figure below depicts the physical differences between a flaccid penis and an erect penis, all of which were known by June 9, 1993.



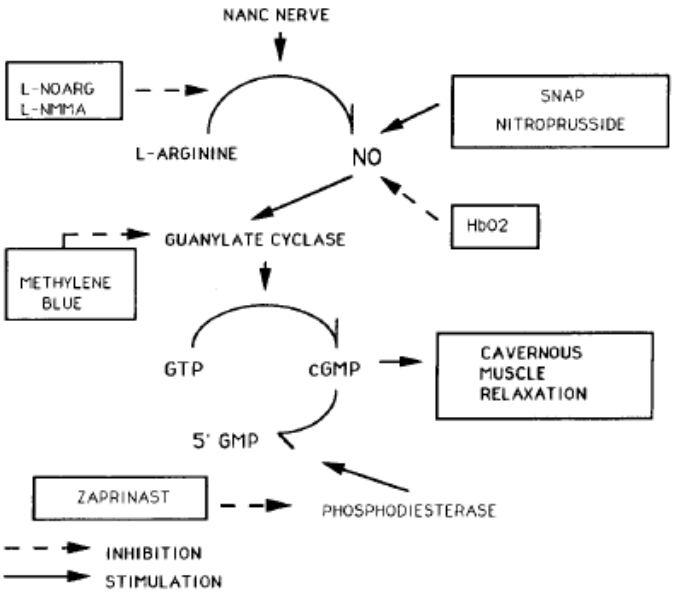
Tr. 130:21-133:11 (Corbin); PTX 286 at Fig. 4 (Corbin 1999).

124. Human erectile function requires the relaxation of smooth muscles in the walls of the arteries that supply blood to the penis and smooth muscles in the spongy erectile tissue in the corpora cavernosa that run the length of the penis. DX 2241 at 8-12 (Wagner 1981); Trial Tr. 130:21–133:2 (Corbin), 206:18–207:14 (Carson). That relaxation results from increases in cGMP levels in the smooth muscle tissue. Trial Tr. 133:12-135:14 (Corbin), 204:11–205:21 (Carson).

125. The pathway that regulates cGMP levels in the penis has been depicted schematically as follows:



DX 2138A at 152, Fig. 1 (Murray 1993).



DX 2221A at 875, Fig. 6 (Trigo Rocha II 1993).

126. Sexual stimulation by sight or through touch or other senses stimulates parasympathetic NANC nerves that trigger the release of NO in a reaction that causes an amino acid called L-arginine to be converted to NO. Trial Tr. 133:12-135:14 (Corbin), 203:1-206:2

(Carson); DX 2170A at 848 (Ignarro 1990); DX 2109A at 90 (Rajfar 1992); DX 2165 at 5-7, 151-152 (Bush Dissertation).

127. That NO permeates the cells of the smooth muscle tissue in the penis and activates the enzyme guanylate cyclase. Trial Tr. 133:12-22 (Corbin), 204:11–205:24 (Carson); DX 2165 at 5-7, 151-152 (Bush Dissertation).

128. When the guanylate cyclase enzyme is activated, it catalyzes the conversion of GTP to cGMP and increases levels of cGMP in the smooth muscle. Trial Tr. 134:1-135:14 (Corbin), 204:11–205:24 (Carson); DX 2165 at 5-7, 151-152 (Bush Dissertation).

129. The increased level of cGMP activates PKG, which phosphorylates several proteins to cause lowering of the intracellular calcium. Trial Tr. 122:22-123:6 (Corbin); DX 2138A at 152, Fig. 1 (Murray 1993); DX 2461 at 25 (Murad 1994).

130. Smooth muscle contraction is dependent on calcium levels. Increases in calcium levels cause contraction of the smooth muscle cells; decreases calcium levels (caused by parasympathetic nerve stimulation) cause relaxation of the smooth muscle. Therefore, the decrease in intracellular calcium brought about by the increase in cGMP levels results in relaxation of smooth muscle cells. DX 2461 at 25 (Murad 1994).

131. Relaxation of the smooth muscle in the arteries that supply blood to the penis allows those arteries to dilate. Trial Tr. 130:21-133:25 (Corbin), 206:25–207:14 (Carson). That dilation increases the flow of blood to fill the cavities in the corpora cavernosa. Trial Tr. 130:21-133:25 (Corbin), 206:25–207:14 (Carson). As the corpora cavernosa expand they exert pressure on the tunica albuginea that impinges on and pinches off veins that would ordinarily allow blood to flow out of the penis. The result is an erection. Trial Tr. 130:21-133:25 (Corbin), 206:25-207:14 (Carson); DX 2221A at 872 (Trigo Rocha II 1993).

132. Phosphodiesterases that degrade cGMP, particularly PDE5, act to lower cGMP levels in the cell by converting cGMP into an inactive compound that does not activate protein kinase and therefore does not relax smooth muscle. Trial Tr. 134:1-135:14 (Corbin), Trial Tr. 207:15-208:3 (Carson). DX 2257 at 153 (Beavo 1990); DX 2138A at 151-152 (Murray 1993); DX 2221A at 875 (Trigo Rocha II).

133. By June 9, 1993, it was known that elevation of cAMP in penile smooth muscle produces erection by a mechanism similar to the mechanism described above for cGMP. DX 2221A at 876 (Trigo-Rocha II 1993). It was believed, however, that the principal intracellular pathway in cavernous smooth muscle relaxation and erection is the cGMP system, and that the cAMP system plays only a minor role in cavernous smooth muscle relaxation and erection. DX 2221A at 876 (Trigo-Rocha II 1993). It further was known that cAMP had many effects in the body, and therefore non-locally injected drugs that acted by elevating cAMP could produce undesirable side effects or safety issues. Trial Tr. 120:23-121:15, 156:2-157:5 (Corbin)

134. By June 9, 1993, it was known that compared to cAMP, cGMP and enzymes involved in cGMP synthesis and breakdown had a more limited body distribution. Trial Tr. 120:23-121:15, 156:2-157:5 (Corbin); DX 2138A at 150-151 (Murray 1993).

135. In June 1993, the belief in the field was that drugs could be developed to specifically target elevation of cGMP by inhibition of PDE5 and that such drugs would not have the same side effect and safety issues as drugs that elevated cAMP levels. Trial Tr. 120:23-121:15, 156:2-158:11 (Corbin), 228:5-17 (Carson).

H. **Synergism / Potentiation**

136. Synergism or potentiation of a pathway means that two signals added together to stimulate a pathway produce a more than an additive effect on the pathway. Trial Tr. 137:23-138:16 (Corbin).

137. In the 1960s, caffeine, a non-selective PDE inhibitor, was shown to have a synergistic effect in the cAMP signaling cascade. Trial Tr. 138:17-139:5 (Corbin); DX 2463 at 208-209, Fig. 6.11 (Robison 1971). Between 1960 and 1993, other synergistic effects between a stimulator and a PDE inhibitor were observed in isolated body tissues for many cAMP and cGMP pathways. Trial Tr. 138:17-139:5 (Corbin).

138. In 1993 it was believed that such potentiation would apply to humans *in vivo*. Trial Tr. 139:10-17 (Corbin), 221:24-222:13 (Carson).

139. Those working in the field in 1993 would have expected a cGMP PDE inhibitor to potentiate the effect of the cGMP signaling cascade in the human penis. Trial Tr. 157:11–158:11 (Corbin), 222:14-223:2 (Carson).

V. THE PERSON OF ORDINARY SKILL IN THE ART TO WHOM THE TEACHINGS OF THE ‘012 PATENT ARE DIRECTED

140. A person of ordinary skill in the art to whom the teachings of the ‘012 patent are directed (“POSA”) would be someone with a Masters degree, Ph.D. or M.D., with a knowledge of physiology, biochemistry, pharmacology, medicinal chemistry, enzymology or urology. The POSA would have an understanding of the role of cyclic nucleotides and their regulation by different PDEs, and an understanding and knowledge of PDE inhibitors and their uses. Trial Tr. 140:7-25 (Corbin), 891:16-892:8 (Goldstein).

VI. THE STATE OF THE ART AS OF JUNE 9, 1993 AND AS OF MAY 13, 1994

A. The Pharmacological Pathway That Controls Penile Erection Was Elucidated Before June 9, 1993 Or May 13, 1994

1. Prior To June 9, 1993 Or May 13, 1994, A POSA Would Have Known That Smooth Muscle Relaxation Of The Corpus Cavernosum Led To Penile Erection

141. In the 1980s, it was discovered that smooth muscle relaxation of the corpus cavernosum is necessary for penile erection. Trial Tr. 119:9–120:1, 143:14-22 (Corbin), 204:11–205:24 (Carson).

142. By the mid-1980s, numerous vasodilatory compounds that were known to relax smooth muscle had been shown to cause erection when injected intracavernosally (*i.e.*, directly into the penis). It was believed that those compounds caused erection by relaxing smooth muscle within the cavernosal space. DX 2226A at 495 (Brindley 1986); DX 2266A at 1025 (Saenz de Tejada 1989).

143. In the late 1980s, certain forms of ED were correlated with an inability to generate enough NO in the endothelium. Saenz de Tejada *et al*. reported in 1989 that diabetic men with ED have an impairment in the release of NO from the endothelium, but do not have a defect in the sensitivity of the corporal smooth muscle to NO. DX 2266A at 1025 (Saenz de Tejada 1989). Saenz de Tejada *et al*. suggested the use of intracavernosal injections of vasodilators for the treatment of ED in diabetics to induce endothelium-independent relaxation in the smooth muscle of the penis that could not otherwise be obtained by the body's natural autonomic and endothelium-dependent mechanisms. DX 2266A at 1025 (Saenz de Tejada 1989).

2. Prior To June 9, 1993 Or May 13, 1994, A POSA Would Have Known That The L-Arginine-Nitric Oxide-Cyclic GMP Pathway Mediates Penile Erection, That cGMP PDE Regulates That Pathway And That A Defect In That Pathway Could Cause ED

144. By June 9, 1993, a POSA would have known that NANC neuron-dependent formation of NO from L-arginine and NO-stimulated production of cGMP by guanylate cyclase play important roles in the mechanism of smooth muscle relaxation in the corpus cavernosum and erection. DX 2221A at 875 (Trigo-Rocha II 1993); Trial Tr. 145:18-22 (Corbin).

145. It was discovered in the 1960s that cGMP is produced from GTP by the enzyme guanylate cyclase. DX 2251 at 404 (Robinson 1971).

146. In the late 1980s, the NANC neurotransmission pathway was identified as the primary mediator of relaxation of corporal smooth muscle and human penile erection. DX 2265A at 9, 11, 13 (Saenz de Tejada 1988). It was understood at that time that sexual stimulation activates the NANC pathway in the human penis. Trial Tr. 133:12-22 (Corbin); DX 2265A at 9, 11, 13 (Saenz de Tejada 1988).

147. Also in the late 1980s, it was discovered that vascular endothelial cells synthesize NO from the amino acid L-arginine. DX 2263A at 664-666 (Palmer 1988).

148. In the early 1990s, a number of papers reported studies in which strips of corpus cavernosum tissue were placed in an organ bath and subjected to electrical field stimulation ("EFS") and a number of test compounds. DX 2170A at 844 (Ignarro 1990); DX 2109A at 90-91 (Rajfer 1992); DX 2176A at 1650-51 (Bush 1992); DX 2165 at 34-37 (Bush Dissertation). EFS was used to mimic sexual stimulation. Trial Tr. 508:17-24 (Corbin). Those organ bath studies would have taught a POSA that the L-arginine-NO-cGMP pathway mediates penile erection, and that a defect in that pathway could cause ED, and potentiation of a portion of that pathway could enhance erectile response. DX 2170A at 848-849 (Ignarro 1990); DX 2109A at

92-94 (Rajfer 1992); DX 2176A at 1651, 1652, 1654 (Bush 1992); DX 2165 at 159-160 (Bush Dissertation); Trial Tr. 173:21-174:16, 293:4-294:24, 295:23-296:19, 299:13-301:13, 305:10-306:12, 310:3-311:7 (Corbin).

149. The organ bath system was a reliable and trustworthy *in vitro* experimental model that had been demonstrated to work in multiple organ systems and in numerous papers since as early as the 1960s. Trial Tr. 163:12-167:9 (Corbin). The organ bath experimental model utilizes a process of "precontracting" tissue, which means that the tissue sample is given a standard level of contraction to overcome the variable levels of contraction/relaxation that intrinsically exist in the tissue. Trial Tr. 489:7-491:16 (Corbin). Once the tissue is precontracted, various compounds may be added to the organ bath to measure the effects of those compounds on the pathway being tested. Trial Tr. 167:10-168:4 (Corbin). Oxygen is bubbled into the organ bath throughout the study to keep the tissue sample alive. Trial Tr. 168:8-13 (Corbin). The relaxation or contraction of the tissue in response to the test compound and EFS is measured. That measurement allows a researcher to determine the effect of the compound on the pathway under investigation. Trial Tr. 168:8-13 (Corbin).

150. Many *in vitro* experimental models, including the organ bath experimental model, are considered reliable by those in the art for predicting what will happen *in vivo* in humans. Trial Tr. 166:14-168:4 (Corbin). The organ bath system is a standard and reliable technique for establishing the effects of test compounds on a particular pathway or mechanism in the tissue sample. Trial Tr. 166:14-168:4 (Corbin). The organ bath system is also standard and reliable *in vitro* model for the intact organism. Trial Tr. 166:14-168:4 (Corbin). A POSA would have reasonably expected that the results in an organ bath study would translate to results *in vivo*. Trial Tr. 163:12-168:4 (Corbin).

151. Organ bath studies allow researchers to isolate and focus on a particular pathway or mechanism, and to control and modify the experimental conditions in a way that would not be possible in an *in vivo* study. Trial Tr. 164:7-165:13 (Corbin). For example, the organ bath technique allows researchers to block certain neurotransmission pathways to isolate and study a single pathway, such as the NANC pathway. Trial Tr. 164:7-166:3, 490:13-491:10 (Corbin). It is impossible to study a pathway in such a manner *in vivo*. Organ bath studies are an important step in the path to experiments in intact animals and humans. Trial Tr. 164:7-166:13 (Corbin).

152. In the 1993 timeframe, rabbit penile tissue often was used as a model for man in organ bath studies of penile erection. Research had demonstrated that the rabbit was a reliable model for human penile function. Trial Tr. 169:11-171:2 (Corbin).

(a) Ignarro 1990 (DX 2170A)

153. In 1990, the Ignarro/Rajfer laboratory at UCLA reported that NANC neuron-mediated relaxation of rabbit corpus cavernosum was attributed to NO and cGMP. DX 2170A at 848-849 (Ignarro 1999); Trial Tr. 163:5-9, 168:8-13 (Corbin). That report was published as Ignarro *et al.*, Nitric Oxide and Cyclic GMP Formation Upon Electrical Field Stimulation Cause Relaxation of Corpus Cavernosum Smooth Muscle, 170 BIOCHEM. & BIOPHYS. RES. COMM. 843–850 (1990) ("Ignarro 1990"). DX 2170A (Ignarro 1990). Ignarro 1990 reported an organ bath study of isolated, precontracted strips of rabbit corpus cavernosum in which the role of the NANC pathway was investigated by blocking the cholinergic and adrenergic neurotransmission pathways. Trial Tr. 168:8-16 (Corbin), 543:1-15 (Bush); DX 2170A at 843 (Ignarro 1990). Ignarro 1990 reported that EFS of corpus cavernosum tissue promotes the endogenous formation and release of NO, nitrite (the principal spontaneous oxidation product of NO) and cGMP. DX 2170 at 847-848 (Ignarro 1990); Trial Tr. 171:5-174:16 (Corbin), 545:2-14, 546:1-5 (Bush).

154. Ignarro 1990 also reported that EFS-induced relaxation was inhibited by agents that interfere with the actions or formation of NO, such as methylene blue (an inhibitor of cytosolic guanylate cyclase), oxyhemoglobin (an NO-sequestering agent that inhibits the biological actions of NO) and N^G-nitro-L-arginine and N^G-amino-L-arginine (two structural analogs of L-arginine that inhibit the conversion of endogenous L-arginine to NO by nitric oxide synthase). DX 2170A at 845-846, 848; Trial Tr. 171:14–173:15 (Corbin), 550:25–553:21 (Bush). The inhibitory effects of the two L-arginine analogs were reversed by the addition of excess L-arginine. DX 2170A at 846, 848 (Ignarro); Trial Tr. 171:14-172:25 (Corbin).

155. Those observations led Ignarro 1990 to conclude that a "major target cell action of endogenous NO is likely to be stimulation of intracellular cyclic GMP formation via heme-dependent activation of cytosolic guanylate cyclase[,]" and that "the close association between relaxation and cyclic GMP formation, coupled with the simultaneous accumulation of nitrite in the tissues, support the view that EFS causes NO and cyclic GMP formation in corpus cavernosum." DX 2170A at 848 (Ignarro).

156. Ignarro 1990 taught a POSA that EFS of the NANC neurotransmission pathway of rabbit corpus cavernosum causes NO release and a large increase in the level of cGMP in the tissue. DX 2170A at 848-849 (Ignarro 1990); Trial Tr. 171:5-174:20 (Corbin), 545:2-14; 546:1-5 (Bush). Those effects were accompanied by relaxation of the tissue, suggesting to a POSA that activation of the NANC neurotransmission pathway and the resulting production and release of NO and cGMP causes penile erectile in man. DX 2170A at 848-849 (Ignarro 1990).

157. Ignarro 1990 stated that "[t]his study demonstrates that corporal smooth muscle relaxation elicited by EFS is due to NANC neuron-dependent formation of NO," (DX 2109A at 848 (Ignarro 1990)) and concluded that "[t]he present observations that penile erection may be

mediated by NO generated in response to NANC neurotransmission provides a rational basis for investigation of the etiology and therapy of impotence." DX 2170A at 849.

158. Ignarro 1990 taught a POSA that NO and cGMP play an important role in the mechanism of smooth muscle relaxation of the corpus cavernosum and erection, and disclosed to the POSA the link between the L-arginine-NO-cGMP pathway that mediates penile erection and therapeutic intervention. Trial Tr. 173:21-174:20 (Corbin).

(b) Rajfer 1992 (DX 2109A)

159. In January 1992, the Ignarro/Rajfer laboratory published a paper reporting another organ bath study, this time using corpus cavernosum tissues from humans. DX 2109A at 90, 91, 92 (Rajfer 1992); Trial Tr. 292:3-14. That publication was Rajfer *et al*., *Nitric Oxide as a Mediator of Relaxation of the Corpus Cavernosum in Response to Nonadrenergic, Noncholinergic Neurotransmission,* 326 NEW ENG. J. MED. 90–94 (1992) ("Rajfer 1992"). DX 2109A (Rajfer 1992). In Rajfer 1992, the neurotransmission pathways other than the NANC were chemically blocked in those tissues. Most of the tissue samples came from impotent men. DX 2109A at 90, 91, 92 (Rajfer 1992); Trial Tr. 292:21–293:3 (Corbin).

160. Rajfer 1992 reported that EFS of human corpus cavernosum caused a marked, transient, frequency-dependant relaxation of the tissue, and that stimulation by *S*-nitroso-*N*-acetylpenicillamine ("SNAP"), a NO-releasing compound, caused rapid, complete and concentration-dependent relaxation of the tissue. DX 2109A at 92-93 (Rajfer 1992); Trial Tr. 294:17-295:1 (Corbin), 559:1–560:17 (Bush).

161. Rajfer 1992 reported that the EFS-induced relaxation and NO-induced relaxation were significantly enhanced by the addition of M&B 22,948, a selective inhibitor of cGMP PDE that is also known as zaprinast. DX 2109A at 92-93 (Rajfer 1992); Trial Tr. 556:19-24 (Bush). Zaprinast enhanced the relaxation of the tissue samples from impotent men and the tissue

samples from non-impotent men. DX 2109A at 92-93 (Rajfer 1992); Trial Tr. 557:2-19; 558:14-18 (Bush).

162. Rajfer 1992 also reported that EFS-induced relaxation and NO-induced relaxation were inhibited by methylene blue. DX 2109A at 92 (Rajfer 1992). N^G-nitro-L-arginine and N^G-amino-L-arginine inhibited EFS-induced relaxation; those inhibitory effects were reversed by the addition of excess L-arginine. DX 2109A at 92 (Rajfer 1992); Trial Tr. 293:4–294:17 (Corbin).

163. Those observations led to the conclusion that "the nonadrenergic, noncholinergic L-arginine–nitric oxide pathway may be involved physiologically in mediating penile erection[,]" that "impairment of this pathway could account for the impairment in relaxation elicited by electrical-field stimulation that has been described in certain impotent men[,]" and that "interference with the L-arginine–nitric oxide pathway could be one cause of impotence that is treatable by the administration of direct-acting vasodilators." DX 2109A at 94 (Rajfer 1992); Trial Tr. 298:14–300:18 (Corbin); Terrett Dep. Tr. at 185:9-187:24.

164. Rajfer 1992 taught a POSA that NO and cGMP play important roles in the mechanism of smooth muscle relaxation of the corpus cavernosum and erection in man, and disclosed to the POSA the link between the L-arginine-NO-cGMP pathway that mediates penile erection and therapeutic intervention. Trial Tr. 298:14–301:13 (Corbin); Terrett Dep. Tr. at 185:9-187:24.

(c) Bush 1992 (DX 2176A)

165. In June 1992, the Ignarro/Rajfer laboratory published a paper reporting an organ bath study of isolated, precontracted human and rabbit corpus cavernosum tissues in which the neurotransmission pathways other than the NANC were chemically blocked. DX 2176A at 1650-51 (Bush); Trial Tr. 301:14–303:1 (Corbin). That publication was Bush *et al*., *Nitric Oxide*

is a Potent Relaxant of Human and Rabbit Corpus Cavernosum, 147 J. UROL. 1650–1655 (1992) ("Bush 1992"). DX 2176A (Bush 1992); Trial Tr. 561:9-16 (Bush).

166. In the Bush 1992 study, tissue samples were stimulated using EFS, acetylcholine (a compound that causes endothelium-dependent relaxation of corpus cavernosum), NO or a NO-releasing nitrovasodilator, such as SNAP, sodium nitroprusside or nitroglycerin. In both rabbit and human tissues, NO was the most potent relaxant, followed by nitroglycerin, SNAP and sodium nitroprusside. DX 2176A at 1650-51 (Bush 1992); Trial Tr. 301:14–303:1 (Corbin), 561:17–562:11 (Bush). NO caused a concentration dependent three- to four-fold increase in cyclic GMP levels at concentrations that caused corporal smooth muscle relaxation. DX 2176A at 1652 (Bush 1992); Trial Tr. 561:17–562:11 (Bush). The nitrovasodilators caused a two- to three-fold elevation of cyclic GMP levels in rabbit corpus cavernosum. DX 2176A at 1652 (Bush 1992); Trial Tr. 561:17–562:11 (Bush).

167. Bush 1992 reported that relaxation of corpus cavernosum was enhanced by zaprinast and inhibited by oxyhemoglobin. DX 2176A at 1652 (Bush 1992); Trial Tr. 562:17–563:15 (Bush). Bush 1992 reported that zaprinast enhanced corporal smooth muscle relaxant responses to NO and nitroglycerin "in a synergistic manner." DX 2176A at 1651 (Bush 1992); Tr. 302:18–303:11 (Corbin), 562:17–563:15 (Bush). Figure 3 of Bush 1992, reproduced below, demonstrates that synergistic effect:

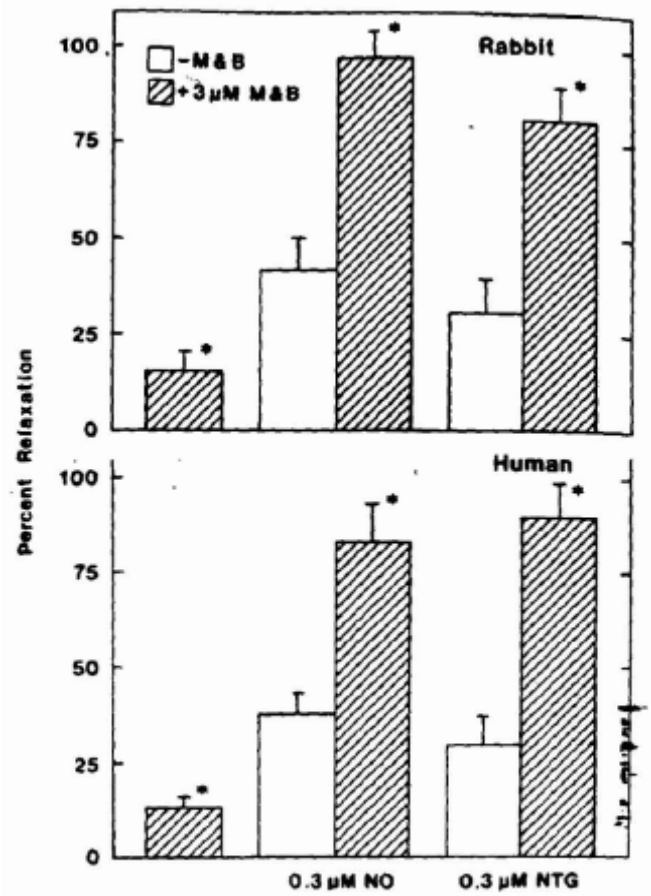


FIG. 3. Augmentation of NO-elicited and nitroglycerin (NTG)-elicited relaxation of strips of rabbit and human corpus cavernosum by M&B 22,948 (M&B). Each point represents the mean ± S.E.M. of 9–12 strips from 4 rabbits or 4 humans. All values in presence of M&B 22,948 are significantly different ($p < 0.01$) from corresponding values obtained in absence of M&B 22,948.

Trial Tr. 157:11-161:25, 302:18-303:11 (Corbin), 562:13–563:15 (Bush); DX 2176A at 1652, Fig. 3 (Bush 1992).

168. A POSA would have understood Figure 3 to demonstrate that the combination of zaprinast and NO or zaprinast and nitroglycerin produced more than an additive effect on relaxation. A POSA would have understood that effect to be synergistic. Trial Tr. 157:11–161:25, 302:18–303:11 (Corbin).

169. Those observations led to the conclusion that "stimulation of nonadrenergic-noncholinergic neurotransmission in corpus cavernosum triggers endogenous formation in NO in either NANC neurons or corporal smooth muscle, which is responsible for the resulting vascular

smooth muscle relaxation[,]" and that "[t]he signal transduction mechanism that links NANC neuronal stimulation to penile erection appears to be NO-elicited activation of cytosolic guanylate cyclase and increased cyclic GMP formation." DX 2176A at 1654 (Bush 1992); Trial Tr. 303:12–304:2, 304:14–305:8 (Corbin).

170. Bush 1992 would have further confirmed to a POSA that NO and cGMP play important roles in the mechanism of smooth muscle relaxation of the corpus cavernosum and erection in man. Trial Tr. 305:10–306:12 (Corbin).

171. Bush 1992 would have suggested to a POSA that a patent and selective PDE5 inhibitor could be used to treat ED. Trial Tr. 306:6-12 (Corbin).

(d) The Bush Dissertation (DX 2165)

172. In 1992, Margaret (Peggy) A. Bush, a co-author of Ignarro 1990, Rajfer 1992 and Bush 1992, was a graduate student in the Ph.D. program in Department of Pharmacology at UCLA, and a member of the Ignarro research group. Trial Tr. 538:11–539:9 (Bush). As part of the requirements of the Ph.D. program, Dr. Bush wrote and defended a doctoral dissertation ("Bush Dissertation"). Trial Tr. 563:17–566:16 (Bush).

173. Dr. Bush's doctoral dissertation, titled "The Role of the L-Arginine-Nitric Oxide-Cyclic GMP Pathway in Relaxation of Corpus Cavernosum and Smooth Muscle," demonstrated that the NANC neuron-elicited formation of NO from L-arginine is responsible for relaxation of isolated strips of precontracted human and rabbit corpus cavernosum, and that cGMP formation mediates relaxation and results from stimulation of guanylate cyclase by NO. DX 2165 at 154, (Bush Dissertation); Trial Tr. 307:17–308:19 (Corbin), 569:18-23, 571:4-14 (Bush). The Bush Dissertation disclosed much of the same organ bath study data reported in Rajfer 1992 and Bush 1992, as well as some additional studies and data. DX 2165 at xiii (Bush Dissertation); Trial Tr. 566:25-567:15 (Bush).

174. In a "Summary and Conclusions" chapter, the Bush Dissertation concludes that "[n]ow that a physiological mechanism for corporal smooth muscle relaxation has been established, this mechanism can be used as a framework to systematically study the problem of impotence[,]" and that "[t]he etiology of vasculogenic and/or neurogenic impotence may be linked to a defect somewhere in the L-arginine-nitric oxide-cyclic GMP pathway." DX 2165 at 159 (Bush dissertation); Trial Tr. 309:11–310:1 (Corbin), 571:22-572:14 (Bush).

175. The Bush Dissertation also concludes that "[e]xpanded knowledge of the physiological mechanism of erection also allows for the design of rational drug therapy for the treatment of disorders such as impotence and priapism." DX 2165 at 159 (Bush Dissertation); Trial Tr. 309:11–310:1 (Corbin), 572:16-19 (Bush). The Bush Dissertation points to the administration of nitrovasodilators by intracavernosal injection or by alternative drug delivery forms as an example of a "very rationale treatment," since nitrovasodilators "would mimic the natural physiological process." DX 2165 at 159 (Bush Dissertation).

176. The Bush Dissertation further concludes that "[k]nowledge of the factors regulating corporal smooth muscle relaxation can be used to critically evaluate the current treatment options for impotence and priapism." DX 2165 at 159 (Bush Dissertation). In that regard, the Bush Dissertation states:

> Clinical development of a specific cyclic GMP phosphodiesterase inhibitor should be considered for the treatment of impotence. A specific cyclic GMP phosphodiesterase inhibitor could enhance corporal smooth muscle relaxation and produce erection by inhibiting the breakdown of cyclic GMP, thus having a direct and specific effect on the L-arginine-nitric-oxide-cyclic GMP mediated relaxation process. Agents that are currently being used to treat impotence, the mechanism of which do not appear to have a physiological basis, should probably be re-evaluated, unless efficacy has been clearly established ...

DX 2165 at 159-160 (Bush Dissertation); Trial Tr. 310:3–311:7 (Corbin), 573:11-24 (Bush).

177. The Bush Dissertation would have taught a POSA that the L-arginine-NO-cGMP pathway is the physiological mechanism that mediates corporal smooth muscle relaxation and penile erection, and would have disclosed to the POSA the link between the L-arginine-NO-cGMP pathway that mediates penile erection and therapeutic intervention. A POSA would have understood the Bush Dissertation to teach that selective inhibitors of cGMP PDEs would have a direct and specific effect on the L-arginine-nitric-oxide-cyclic GMP pathway of increasing cGMP levels. A POSA therefore would conclude that the clinical development of selective inhibitors of cGMP PDE for the treatment of ED would be rationally based on the knowledge of the physiological mechanism of erection and be expected to be effective in the treatment of ED. Trial Tr. 307:17–311:7 (Corbin), Trial Tr. 573:11-24 (Bush).

178. Dr. Bush defended the final draft of the Bush Dissertation before the Doctoral Committee on November 30, 1992. Trial Tr. 564:20-24 (Bush); DX 2456C (Bush Transcript). The Doctoral Committee consisted of several members, including Drs. Ignarro and Rajfer. DX 2456D at 9 (Bush Dissertation Invitation).

179. The Bush Dissertation is prior art to the ‘012 patent. Trial Tr. 575:22–576:13 (Stipulation by Pfizer).

(e) Trigo-Rocha I (DX 2254)

180. In February 1993, Trigo-Rocha *et al*. published an *in vivo* study of the role of NO and cGMP in corporal smooth muscle relaxation in anesthetized dogs. DX 2254 at H419 (Trigo-Rocha I). That publication was Trigo-Rocha *et al., Nitric Oxide and cGMP: Mediators of Pelvic Nerve-Stimulated Erection in Dogs*, 264 AM. J. PHYSIOL. H419–H422 (1993) (“Trigo-Rocha I”). DX 2254 (Trigo-Rocha I). The goal of the study was to determine whether the L-arginine-NO-cGMP pathway, which had been previously shown to mediate neurostimulation-induced smooth muscle relaxation in penile tissue of rabbits and humans *in vitro*, is also

responsible for cavernous smooth muscle relaxation and penile erection *in vivo*. DX 2254 at H419 (Trigo-Rocha I).

181. Trigo-Rocha I reported that the dogs received pelvic nerve stimulation to induce penile erection and intracavernosal injections of various compounds to test their effects on tumescence. DX 2254 at H419 (Trigo-Rocha I). Stimulation-induced penile tumescence was enhanced by zaprinast and SNAP, and inhibited by methylene blue and L-NAME (a structural analog of L-arginine and specific inhibitor of NO synthesis). DX 2254 at H420-421 (Trigo-Rocha I).

182. Trigo-Rocha I concludes that their investigations provide *in vivo* evidence to support the role of the L-arginine-nitric oxide-cGMP pathway in penile erection," (DX 2254 at H421 (Trigo-Rocha I)), and that "pharmacological manipulation of this pathway may offer more effective treatment of impotence and priapism." DX 2254 at H422 (Trigo-Rocha I).

183. Trigo-Rocha I would have further confirmed to a POSA that many of the observations and conclusions made by Ignarro 1990, Rajfer 1992 and Bush 1992 based on *in vitro* evidence would also apply *in vivo*, and disclosed to the POSA a link between the L-arginine-NO-cGMP pathway that mediates penile erection and therapeutic intervention. DX 2254 at H420-2 (Trigo-Rocha I); Trial Tr. 481:21–485:5 (Corbin).

(f) Trigo-Rocha II (DX 2221A)

184. In April 1993, Trigo-Rocha *et al*. published another *in vivo* canine study that provided further evidence that the L-arginine-NO-cGMP pathway mediates cavernous smooth muscle relaxation and penile erection in intact animals. DX 2221A at 872, (Trigo-Rocha II); Trial Tr. 526:10–528:2 (Corbin). That publication was Trigo-Rocha et al., *The Role of Cyclic Adenosine Monophosphate, Cyclic Guanosine Monophosphate, Endothelium and Nonadrenergic*

Neurotransmission In Canine Penile Erection, 149 J. UROL. 872–877 (1993) ("Trigo-Rocha II"). DX 2221A (Trigo-Rocha II).

185. Trigo-Rocha II reported that chemical destruction of the endothelium (a natural source of NO) abolished the erection-inducing effect of acetylcholine, but not the erection-inducing effect of EFS. DX 2221A at 874 (Trigo-Rocha II). From that and other observations, Trigo-Rocha II concluded that NO released from nerve endings plays a major role in erection. DX 2221A at 876 (Trigo-Rocha II).

186. Trigo-Rocha II reported that intracavernous injection (*i.e.*, injection into the penis) of a cGMP analog (8-Br-cGMP) produced a much greater erectile response than did the same dose of a cAMP analog (8-Br-cAMP). DX 2221A at 875 (Trigo-Rocha II). From that and other observations, Trigo-Rocha II concluded that "cyclic GMP is a more important second messenger or intracellular transmitter for cavernous smooth muscle relaxation[,]" and that "the cyclic AMP system … plays a minor role in cavernous smooth muscle relaxation and erection." DX 2221A at 876 (Trigo-Rocha II).

187. Trigo-Rocha II disclosed the following schematic of the L-arginine-NO-cGMP pathway that mediates cavernous smooth muscle relaxation:

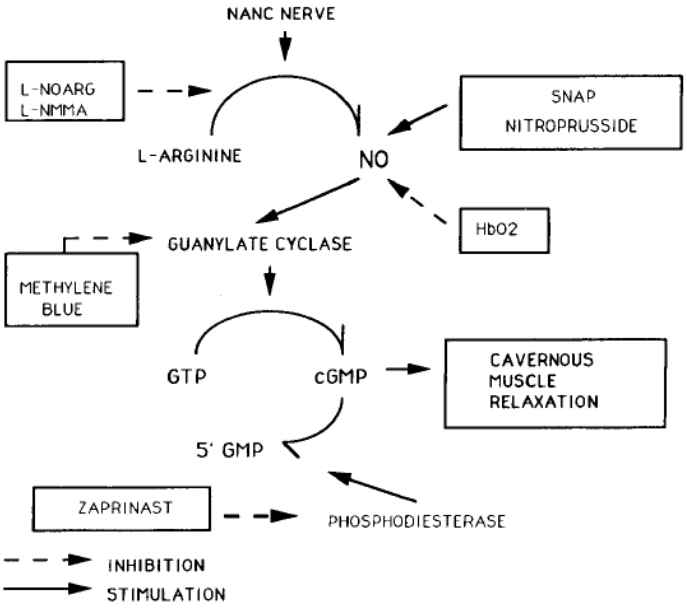


FIG. 6. Cyclic GMP pathway: Nitric oxide (NO) is released from L-arginine upon activation of NANC nerve, a step inhibited by N-nitro-L-arginine (L-NOARG) and N-monomethyl-L-arginine (L-NMMA). NO can also be released from a NO-releasing substance such as nitroprusside. Nitric oxide then penetrates smooth muscle cell and activates guanylate cyclase, which transforms GTP into cGMP. This signals protein kinase to cause smooth muscle relaxation. Methylene blue inhibits this process by inhibiting guanylate cyclase, and oxyhemoglobin works as a scavenger of NO. cGMP is converted to GMP by phosphodiesterase, an enzyme that can be inhibited by Zaprinast.

DX 2221A at 875, Fig. 6 (Trigo-Rocha II).

188. A POSA would have understood the schematic to disclose that the L-arginine-NO-cGMP pathway entails the following:

- Upon activation of the NANC nerve, L-arginine releases NO (a step which can be inhibited by structural analogs of L-arginine such as L-NOARG or L-NMMA);
- NO penetrates the smooth muscle cell and activates guanylate cyclase (a step which can be inhibited by oxyhemoglobin, or enhanced or activated by NO-releasing nitrovasodilators such as SNAP or sodium nitroprusside);
- Guanylate cyclase transforms GTP into cGMP (a step which can be inhibited by methylene blue);
- Cyclic GMP signals protein kinase to cause cavernous smooth muscle relaxation;
- Phosphodiesterase regulates the production of cGMP by converting cGMP into 5'-GMP (a step which can be inhibited by cGMP PDE inhibitors such as zaprinast).

Trial Tr. 134:1–135:14, 144:14–149:22 (Corbin).

3. Prior To June 9, 1993 Or May 13, 1994, A POSA Would Have Known That A Selective PDE5 Inhibitor Would Potentiate The Effects Of Nitric Oxide And Thereby Enhance The Accumulation Of Cyclic GMP And Relaxation Of Smooth Muscle In The Corpus Cavernosum

189. Before June 9, 1993 and/or before May 13, 1994, several prior art references had suggested the use of selective PDE5 inhibitors for the treatment of ED.

190. In the 1993–1994 timeframe, zaprinast was the most studied cGMP PDE inhibitor, and the most potent and selective PDE5 inhibitor in public use. Trial Tr. 558:20-25 (Bush); DX 2138A at 151, 154-155 (Murray 1993). Zaprinast had been reported to have an IC_{50} value for inhibition of PDE5 in the range of about 100–1,100 μM. Trial Tr. 129:22-130:2, 149:23-151:8; DX 2138A at 152, 154 (Murray 1993). Although sildenafil and other PDE5 inhibitors that are one to two orders of magnitude more potent and selective for PDE5 than zaprinast were publicly disclosed by Pfizer before June 9, 1993, (Trial Tr. 331:14-333:4, 336:1-337:2, 341:13-342:20 (Corbin)), those PDE5 inhibitors were not in use by anyone outside of Pfizer or its research partners. Trial Tr. 279:14-280:2 (Carson).

(a) Rajfer 1992 (DX 2109A)

191. Rajfer 1992 reported that zaprinast significantly enhanced cGMP levels and smooth muscle relaxation in human corpus cavernosum tissue in response to EFS or NO. Trial Tr. 296:20–297:19 (Corbin); DX 2109A at 92 (Rajfer 1992).

192. A POSA would have understood Rajfer 1992 to teach that a selective PDE5 inhibitor, such as zaprinast or another selective PDE5 inhibitor, would potentiate the effects of NO and thereby enhance the accumulation of cGMP and relaxation of smooth muscle in the corpus cavernosum. Trial Tr. 299:13–19, 300:25–301:13 (Corbin); Terrett Dep. Tr. at 154:12-16, 155:10-11, 172:2-7, 172:11-16.

193. A POSA would have known from Rajfer 1992 that a potent and selective inhibitor of PDE5 would be useful in the treatment of ED. Trial Tr. 300:25–301:13 (Corbin); Terrett Dep. Tr. at 154:12-16, 155:10-11, 172:2-7, 172:11-16.

194. A POSA would have understood that the Rajfer 1992 paper used words like "suggest" and "conceivable" because scientists are very conservative, and because reviewers and editors often will not allow the scientist/author to use more definitive language. Trial Tr. 299:21-300:18 (Corbin).

(b) Bush 1992 (DX 2176A)

195. Bush 1992 reported that zaprinast significantly and synergistically enhanced cGMP levels and smooth muscle relaxation in human and rabbit corpus cavernosum tissue in response to EFS or NO. DX 2176A at 1651 (Bush 1992); Trial Tr. 157:11-161:25, 302:18–303:11 (Corbin).

196. A POSA would have understood Bush 1992 to teach that a selective PDE5 inhibitor, such as zaprinast or another selective PDE5 inhibitor, would potentiate the effects of NO and thereby enhance the accumulation of cGMP and relaxation of smooth muscle in the corpus cavernosum. Trial Tr. 305:10-306:12 (Corbin).

197. A POSA would have known from Bush 1992 that a potent and selective inhibitor of PDE5 would be useful in the treatment of ED. Trial Tr. 306:6-12 (Corbin).

(c) The Bush Dissertation (DX 2165)

198. The Bush Dissertation taught that zaprinast significantly and synergistically enhanced cGMP levels and smooth muscle relaxation in human and rabbit corpus cavernosum tissue in response to EFS or NO. Trial Tr. 157:11–158:6 (Corbin). *See* DX 2165 at 98 (Fig. 2.22) (Bush Dissertation).

199. A POSA would have understood the Bush Dissertation to teach that a selective PDE5 inhibitor, such as zaprinast or another selective PDE5 inhibitor, would potentiate the effects of NO and thereby enhance the accumulation of cGMP and relaxation of smooth muscle in the corpus cavernosum. Trial Tr. 307:17–311:7 (Corbin).

200. The Bush Dissertation recommended that drug therapies for the treatment of ED should be rationally designed based on the expanded knowledge of the physiological mechanism of erection, and that any ED treatments whose mechanism does not appear to have a physiological basis should be reevaluated unless efficacy has been clearly established. DX 2165 at 159 (Bush Dissertation); Trial Tr. 307:17–311:7 (Corbin).

201. The Bush Dissertation explicitly recommended the clinical development of specific cGMP PDE inhibitors for the treatment of ED. DX 2165 at 159-160 (Bush Dissertation). The Bush Dissertation reasoned that a specific cGMP PDE inhibitor would enhance corporal smooth muscle relaxation and produce erection by inhibiting the breakdown of cGMP, thus having a direct and specific effect on the L-arginine-NO-cGMP mediated relaxation process. DX 2165 at 159-160 (Bush Dissertation); Trial Tr. 307:17–311:7 (Corbin).

202. A POSA would have known from the Bush Dissertation that a potent and selective inhibitor of PDE5 would be useful in the treatment of ED. Trial Tr. 307:17–311:7 (Corbin).

(d) Murray 1993 (DX 2138A)

203. Murray, *Phosphodiesterase V_A Inhibitors,* 6 DRUG NEWS & PERSP. 150–156 (1993) ("Murray 1993"), which published in April 1993, is a review article concerning the state of the art of the therapeutic use of PDE5 inhibitors. DX 2138A (Murray 1993).

204. Murray 1993 indicated that there was a "logical foundation" for selective PDE inhibitors to be used to target specific tissues or organs. DX 2138A at 150 (Murray 1993).

Murray 1993 gave the example of milrinone, a PDE3 inhibitor that was already approved for oral use to treat congestive heart failure. DX 2138A at 150 (Murray 1993).

205. Murray 1993 discloses that the effects of the PDE5 inhibitor zaprinast have been studied in a number of smooth muscle types. DX 2138 at 151-152 (Murray 1993).

206. Murray 1993 discloses that zaprinast had been administered safely in a clinical setting in man and had been administered orally. DX 2138 at 154 (Murray 1993).

207. Murray 1993, referencing Rajfer 1992, discloses that "[w]ith strips of human corpus cavernosum, zaprinast alone caused a relaxation and enhanced the relaxation caused by nitric oxide or electrical stimulation." DX 2138A at 153 (Murray 1993). A POSA would have understood Murray 1993 to teach that zaprinast had been shown to enhance cGMP production and corporal smooth muscle relaxation caused by NO or EFS. Trial Tr. 153:21-154:5 (Corbin).

208. Murray 1993 states: "Smooth muscle relaxation appears to be the most promising of the potential uses of PDE V_A inhibitors, and possible therapeutic utilities include vasodilatation, bronchodilatation, modulation of gastrointestinal motility and treatment of impotence." DX 2138A at 154-155 (Murray 1993). A POSA would have understood Murray 1993 to teach that the treatment of ED is a promising therapeutic utility of selective PDE V_A (PDE5) inhibitors. Trial Tr. 158:7-11, 321:14-19 (Corbin); DX 2137 (May 26, 1993 Terrett Memo); DX 2108 at PFZ00706667 (July 1993 ECMT Memo); Terrett Dep. Tr. at 232:9-20.

209. Murray 1993 states: "The combination of a limited tissue distribution and substrate specificity suggests that a specific PDE V_A inhibitor could have a narrow range of physiological and pharmacological actions." DX 2138A at 151 (Murray 1993).

210. Murray 1993 taught that PDE5 was known to be cGMP-specific and to have a limited distribution in body tissues, suggesting "that a specific PDE V_A inhibitor could have a

narrow range of physiological and pharmacological actions." DX 2138A at 151 (Murray 1993). As such, a POSA would have expected a selective PDE5 inhibitor to have a narrow range of pharmacological actions and thus few side effects. Trial Tr. 313:15-318:18 (Corbin).

211. Murray 1993 disclosed that "selective actions could be achieved by virtue of the fact that many of the effects of PDE V_A inhibitors in a particular tissue are dependent on the level of guanylate cyclase activity (see Fig. 1)." DX 2138 at 155 (Murray 1993).

212. Figure 1 of Murray, reproduced below, illustrates and describes the pathway cGMP metabolism in nonretinal cells:

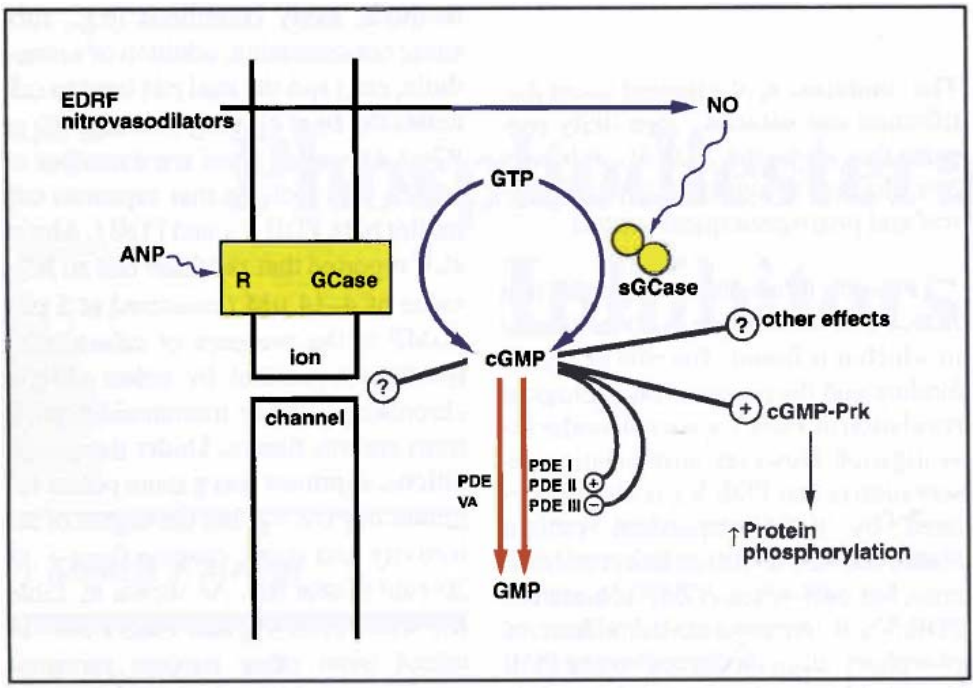


Fig. 1. cGMP metabolism in nonretinal cells. The pathways for the synthesis and breakdown of cGMP are shown in blue and red, respectively. The potential mechanisms by which cGMP can alter cell function are shown in green. It is not intended to imply that all the enzymes and routes shown are present in every cell type. Indeed, the diversity between tissues can contribute to the selectivity of PDE V_A inhibitors. Selective action of PDE V_A inhibitors may be obtained by a number of mechanisms, for example, the tissue distribution of PDE V_A itself, and also that of the other PDE isoenzymes, and by the activity of guanylate cyclase. ANP, atrial natriuretic peptide; EDRF, endothelial-derived relaxing factor; (s)GCase, (soluble) guanylate cyclase; cGMP-PrK, cGMP-dependent protein kinase.

DX 2138A at 152 (Murray 1993).

213. A POSA would have understood Figure 1 of Murray 1993 to disclose that the pathway that controls smooth muscle relaxation includes: (1) activation of guanylate cyclase by NO; (2) production of cGMP from GTP by guanylate cyclase; (3) activation of cGMP-dependant protein kinase by cGMP, which leads to the physiological response of smooth muscle relaxation; and (4) metabolism of cGMP into inactive GMP by PDE5. Terrett Dep. Tr. at 107:8-23; Trial Tr. 133:23-135:14 (Corbin).

214. Murray 1993 states: "Thus, PDE V_A inhibitors will have the greatest effect in cells and tissues that have a high guanylate cyclase activity, and there could be considerable value in a therapeutic agent that has little activity in its own right, but potentiates the effects of endogenous mediators." DX 2138A at 155 (Murray 1993).

215. A POSA also would have understood that NO generation resulting from sexual stimulation is an endogenous mediator of guanylate cyclase activity, and would have understood Murray 1993 to teach that there could be considerable value in a PDE5 inhibitor that has little activity in its own right, but potentiates the effects of NO. Trial Tr. 304:14-305:8, 321:14-18, 317:6-319:6, 320:25-321:19, 376:4-18 (Corbin); Terrett Dep. Tr. at 232:9-20.

216. A POSA would have understood Murray 1993 to teach that a selective PDE5 inhibitor would target guanylate cyclase activity in the body, and have its greatest effect in those tissues having high guanylate cyclase activity. Trial Tr. 316:23–318:18, 320:25–321:13 (Corbin).

217. A POSA would have known that during sexual stimulation, there is constant creation of NO in the corpus cavernosum. Trial Tr. 204:3-205:10, 224:25-225:5 (Carson). A POSA would have understood that sexual stimulation increases guanylate cyclase activity in the corpus cavernosum by increasing the production and release of NO. Trial Tr. 205:11-205:21,

225:5-14 (Carson). A POSA would have recognized that corpus cavernosum has "high guanylate cyclase activity" during sexual stimulation and is the type of tissue in which a selective PDE5 inhibitor would have its greatest effect. Trial Tr. 316:23–318:18, 320:25–321:13 (Corbin).

218. A POSA would have reasonably expected that during sexual stimulation, the level of guanylate cyclase activity in the penis would increase significantly relative to the level of guanylate cyclase activity in other tissues in the body. Trial Tr. 319:4-6 (Corbin). A POSA would have understood that a selective PDE5 inhibitor would target that increased level of guanylate cyclase activity in the penis. Trial Tr. 316:23–318:18, 320:25–321:13 (Corbin).

219. A POSA would have understood Murray 1993 to teach that a selective PDE5 inhibitor, such as zaprinast or another selective PDE5 inhibitor, would potentiate the effects of NO and thereby enhance the accumulation of cGMP and relaxation of smooth muscle in the corpus cavernosum. Trial Tr. 321:14-18 (Corbin); Terrett Dep. Tr. at 232:9-20.

220. A POSA would have known from Murray 1993 that a potent and selective inhibitor of PDE5 would be useful in the treatment of ED. Trial Tr. 321:14-18 (Corbin); Terrett Dep. Tr. at 232:9-20.

221. A POSA would have understood that Murray 1993 phrases such as "potential uses" and "possible therapeutic utilities" when describing uses and utilities for PDE5 inhibitors because scientists are usually pretty conservative in what they write. Trial Tr. 377:14-24 (Corbin). A POSA would expect to see that type of language. Trial Tr. 377:14-24 (Corbin).

4. Prior To June 9, 1993 Or May 13, 1994, A POSA Would Have Believed That Human Corpus Cavernosum Tissue Contains Three PDE Isozymes – PDE3, PDE4 And PDE5 – And Would Have Recognized That PDE5 Was The Only cGMP PDE Present In That Tissue

222. Before June 9, 1993, it had been reported that human corpus cavernosum tissue contains three PDE isozymes: PDE3, PDE4 and PDE5. DX 2172A (Taher 1993).

(a) Taher 1993 (DX 2172A)

223. In April 1993, Taher *et al*. reported that they had found PDE III (cGMP inhibited); PDE IV (cAMP specific); and PDE V (cGMP-specific) in the human corpus cavernosum. DX 2172A. That report was published as Taher *et al*., *Phosphodiesterase Activity in Human Cavernous Tissue and the Effect of Various Selective Inhibitors*, 149 J. UROL. 285 (1993). DX 2172A (Taher 1993).

224. Taher 1993 reported that selective inhibitors of PDE III, PDE IV and PDE V relaxed precontracted strips of human corpus cavernosum tissue dose-dependently in an organ bath study. DX 2172A (Taher 1993).

225. A POSA would have known from Taher 1993 that human corpus cavernosum tissue contains PDE3, PDE4 and PDE5. Trial Tr. 154:15–155:18 (Corbin), 208:15-24, 226:4-11 (Carson), 774:15-775:1 (Ellis).

226. Taher 1993 did not report that PDE1 is present in human corpus cavernosum tissue. DX 2172A (Taher 1993).

227. A POSA would have recognized from Taher 1993 that PDE5 is the only cGMP PDE present in human corpus cavernosum tissue. Trial Tr. 155:19-21 (Corbin); 208:15-209:6 (Carson), 346:5-7 (Corbin); 932:12-933:7, 949:15-23 (Goldstein).

228. A POSA would have recognized that the ability of zaprinast to enhance relaxation of corpus cavernosum tissue in response to NO or EFS, as reported in Rajfer 1992, Bush 1992

and the Bush Dissertation, was due to zaprinast's inhibitory activity against PDE5, not due to its inhibitory activity against PDE1. Trial Tr. 152:22–156:1 (Corbin).

229. Taher 1993 stated that PDE III inhibitor was the most potent PDE inhibitor and possesses an EC_{50} equal to papaverine. DX 2172A at 28 (Taher 1993). A POSA would have understood that statement to mean that, compared to the PDE IV inhibitor and PDE V inhibitor used in the study, PDE III inhibitor was more potent as a PDE inhibitor. Trial Tr. 156:2-157:5 (Corbin); PTX 0004 at PFZFH 01206 (Saenz de Tejada Declaration). That statement alone would not have taught a POSA which PDE isoenzyme was predominant in the human corpus cavernosum, or which PDE isoenzyme was the best target for drug in treating ED. PTX 0004 at PFZFH 01206 (Saenz de Tejada Declaration).

230. The Taher abstract would not have encouraged a POSA to use a PDE3 inhibitor to treat ED. Trial Tr. 156:2–157:10 (Corbin).

231. A POSA also would have known, based on the work of Trigo Rocha *et al.*, that cGMP is a more important second messenger for relaxation of smooth muscle in human penile tissue. PTX 0004 at PFZFH 01206 (Saenz de Tejada Declaration); DX 2221A at 876 (Trigo-Rocha II). Based on the that teaching, a POSA would have focused more on cGMP PDEs, such as PDE5, than cAMP PDEs, such as PDE3 and PDE4. PTX 0004 at Saenz de Tejada Declaration at PFZFH 01206.

232. Taher 1993 concludes: "Our findings support the involvement of cyclic nucleotide metabolism in the regulation of cavernous smooth muscle tone and open a possibility of using selective PDE inhibitor[s] in treating erectile dysfunction." DX 2172A (Taher 1993).

B. A POSA Would Have Been Motivated To Orally Administer A Potent And Selective PDE5 Inhibitor To Treat ED And Would Have Reasonably Expected That Such Administration Would Be Effective For Treating ED

233. A POSA would have been motivated to orally administer a potent and selective PDE5 inhibitor, such as sildenafil or any of the other especially preferred compounds of EP '756 or EP '004, for the treatment of ED because, compared to other routes of administration, oral administration generally is more convenient, safer and enhances patient compliance. Trial Tr. 216:1-10, 219:5-10 (Carson), 367:9-18 (Corbin).

234. The advantages associated with oral administration led ED investigators in the 1993–1994 timeframe to actively search for compounds that could be administered orally for the treatment of ED. For example, the NIH Consensus Statement from the December 7–9, 2002 NIH Consensus Development Conference on Impotence recommended the development of new ED therapies, with an emphasis on the development of oral pharmacologic agents. DX 2462 at 194 (NIH Consensus Statement); Trial Tr. 217:12–218:5 (Carson).

235. It was recognized in 1990 that an oral treatment for ED could be accomplished by creating a drug that has selectivity for the penile tissue responses, and that basic science studies on the pharmacologic control of neurotransmission with the corpora cavernosa had recently been initiated with the hope of identifying some unique characteristics of neurotransmission in the penile vasculature. PTX 40 at 110 (Foreman 1990).

236. A POSA would have reasonably expected that sildenafil, or any of the other especially preferred compounds of EP '756 or EP '004, could be administered orally for the treatment of ED, and that those compounds would be effective when orally administered for the treatment of ED, because EP '756 and EP '004 disclosed oral administration of those compounds for the treatment of numerous different conditions. DX 2074 at 7:23-25 (EP '756); DX 2006 at 9:11-24 (EP '004); Trial Tr. 218:6-219:2; 219:25-220:11 (Carson), 367:19-368:10 (Corbin). The

disclosure of oral administration of those compounds in EP '756 and EP '004 would have suggested to a POSA that those compounds are effectively absorbed and reach effective tissue concentrations when orally administered. Trial Tr. 218:6-219:2, 219:25–220:11 (Carson), 368:14-369:5 (Corbin).

237. A POSA also would have reasonably expected that sildenafil, or any of the other especially preferred compounds of EP '756 or EP '004, could be administered orally for the treatment of ED, and that those compounds would be effective when orally administered for the treatment of ED, because PDE inhibitors had been administered orally for decades by June 9, 1993. Trial Tr. 221:7–222:13 (Carson), 367:23–369:5 (Corbin). For example, theophylline, a non-selective PDE inhibitor, had been administered orally to treat asthma. Trial Tr. 221:7-23 (Carson). Pentoxifylline, another non-selective PDE inhibitor, was used orally for the treatment of peripheral vascular disease, and by June 9, 1993 had been demonstrated to have effectiveness in the treatment of ED when administered orally. DX 2259 at 363 (Korenman 1993); DX 2262 at 65 (Morley 1993). By June 9, 1993, the selective PDE3 inhibitor milrinone had been used orally to treat congestive heart failure. Trial Tr. 221:7-23 (Carson), 367:23–368:12 (Corbin). As a selective PDE3 inhibitor, it was absorbed orally, reached target tissue levels and was safe and effective. Trial Tr. 221:7-23 (Carson), 367:23-368:12 (Corbin). By June 9, 1993, PDE5 inhibitors such dipyridamole and zaprinast had demonstrated PDE5-inhibiting effects when administered orally. Trial Tr. 253:25-254:6 (Carson), 367:23–369:5 (Corbin).

238. EP '004 discloses oral administration and does not disclose any side effect resulting from the administration of the disclosed compounds. Trial Tr. 348:21-349:5, 350:7-351:4 (Corbin); DX 2006 (EP '004).

239. EP ‘756 does not disclose any side effects resulting from the oral administration of the disclosed compounds or resulting from inhibition of PDE1 upon administration of the disclosed compounds. Trial Tr. 218:14-219:10 (Carson), 367:9-18, 368:14-369:5, 505:15-25 (Corbin); DX 2074 (EP '756).

240. A POSA would have reasonably expected a potent and selective PDE5 inhibitor to be effective orally for the treatment of vascular diseases, including ED, and would not have considered intracavernosal injection to be required. Trial Tr. 222:14–223:2 (Carson). A POSA would have reasonably expected an orally administered potent and selective PDE5 inhibitor to be readily absorbed, reach the corpus cavernosum, penetrate into the corporal smooth muscle cells and cause relaxation of that tissue. Trial Tr. 223:3-15, 224:9–225:14 (Carson).

241. PDE5 inhibitors enhance the relaxation of smooth muscle in vascular tissue by increasing cGMP levels. Trial Tr. 226:19–227:16 (Carson). Relaxation of the smooth muscle in vascular tissue results in dilation of that vascular tissue, i.e., vasodilation. Trial Tr. 226:19–227:16 (Carson).

242. U.S. Patent No. 4,931,445 (“the ‘445 patent”) is titled: “Agents For Treatment Of Male Impotence.” DX 2191. It issued on June 5, 1990. DX 2191. It is prior art to the ‘012 patent and would have been available to a POSA prior to June 1993. Trial Tr. 779:16-780:5 (Ellis), 950:9-15 (Goldstein).

243. The abstract of the ‘445 patent states: “Etoperidone and its pharmaceutically acceptable salts are useful in the treatment of male sexual impotence.” DX 2191 (‘445 patent).

244. The ‘445 patent teaches the POSA the use of etoperidone for the treatment of male sexual impotence: “The process of the present invention is intended for treatment of male impotence. The process essentially involves administration of etoperidone or a pharmaceutically

acceptable acid addition salt thereof, to a male mammal in need of such treatment." DX 2191 at 2:46-50 ('445 patent); Trial Tr. 951:15-952:1 (Goldstein). Treatment of a male mammal includes treatment of a male human. Trial Tr. 781:10-22 (Ellis).

245. The '445 patent teaches that etoperidone has hypotensive activity. DX 2191 at 1:20-21 ('445 patent). Hypotensive compounds reduce blood pressure, like antihypertensives. Trial Tr. 781:4-9 (Ellis), 951:13-14 (Goldstein).

246. The '445 patent teaches that oral administration of etoperidone for the treatment of male sexual impotence is a preferred route of administration, being both effective and harmless: "Administration of etoperidone according to the present invention may be made by the parenteral, oral or rectal routes. Although oral administration of etoperidone is a preferred route of administration, being both effective and harmless for most patients, nonetheless a parenteral method of administration, direct injection into the penis, is the most preferred route of administration for practice of the method of this invention." DX 2191 at 2:60-67 ('445 patent).

247. The '445 patent states that "The effectiveness of etoperidone in the induction of penile erections was determined in an *in vivo* animal model." DX 2191 at 2:50-52 ('445 patent). The '445 patent indicates that the *in vivo* test involved intracavernosal injection of etoperidone into the penises of rabbits and resulted in rigid erections. DX 2191 at 2:50-56, 4:1-28 ('445 patent); Trial Tr. 952:2-17 (Goldstein).

248. The '445 patent does not provide any results from tests involving oral administration or involving humans. DX 2191 ('445 patent); Trial Tr. 954:13-21 (Goldstein).

249. Claims 2-5 of the '445 patent (which depend directly or indirectly from claim 1) expressly claim oral administration of etoperidone to treat male sexual impotence. DX 2191 at 4:30-43 ('445 patent); Trial Tr. 783:4-13 (Ellis), 956:17-957:17 (Goldstein).

250. One of the named inventors of the ‘445 patent is Dr. Inigo S. de Tejada. DX 2191 (‘445 patent). Dr. de Tejada had the knowledge and training of a person of ordinary skill in the art at the time the ‘445 patent was filed. Trial Tr. 780:15-24 (Ellis).

251. Pfizer’s expert, Dr. Goldstein, is one of the named inventors of the ‘445 patent. DX 2191 (‘445 patent); Trial Tr. 780:6-14 (Goldstein). Dr. Goldstein has the knowledge and training of a person of ordinary skill in the art. Trial Tr. 780:6-14 (Goldstein). Dr. Goldstein’s work on the ‘445 patent predated his work with Pfizer on sildenafil or Viagra. Trial Tr. 950:9-15 (Goldstein).

252. Dr. Goldstein signed a declaration when the application for the ‘445 patent was filed stating that he had read and understood the specification and claims of the application for the ‘445 patent. DX 2193 at page 1 of declaration (Goldstein declaration); Trial Tr. 950:16-951:4 (Goldstein).

253. Dr. Goldstein does not recall ever telling his patent attorney that he did not think that oral administration of etopenidone to a human would treat ED. Trial Tr. 955:22-956:16 (Goldstein).

254. Dr. Goldstein does not recall ever telling his patent attorney that he thought that oral administration of etopenidone to treat ED, as claimed in his ‘445 patent, would not be an effective method of treating ED. Trial Tr. 955:22-956:16 (Goldstein).

255. Dr. Goldstein does not recall ever telling the Patent Office that he did not think that oral administration of etopenidone to a human would treat ED. Trial Tr. 955:22-956:16 (Goldstein).

256. Dr. Goldstein does not recall ever telling the Patent Office that he thought that oral administration of etopenidone to treat ED, as claimed in his '445 patent, would not be an effective method of treating ED. Trial Tr. 955:22-956:16 (Goldstein).

257. During reexamination of the '012 patent, the Board of Patent Appeals and Interferences found, based upon a preponderance of record, that oral administration of etopenidone is an effective ED therapy. DX 2303 at 7, 40-41 (finding of fact 91), 50 (February 12, 2010 BPAI Decision).

258. U.S. Patent No. 4,687,771 ("the '771 patent") is titled: "Method For Treatment Of Male Impotence." DX 2189 ('771 patent). It issued on August 18, 1987. DX 2189 ('771 patent). It is prior art to the '012 patent and would have been available to the POSA prior to June 1993.

259. The abstract of the '771 patent states: "Trazadone and its pharmaceutically acceptable salts are useful in the treatment of male sexual impotence." DX 2189 ('771 patent).

260. The '771 patent teaches the use of trazadone for the treatment of male sexual impotence: "This invention concerns a novel therapeutic treatment for male sexual impotence by the administration of 'trazadone'" (DX 2189 at 1:13-15 ('771 patent)); "The process of the present invention is intended for treatment of male impotence. The process essentially involves administration of trazodone." DX 2189 at 3:13-15 ('771 patent).

261. The '771 patent teaches that trazodone has hypotensive activity. DX 2189 at 1:17-20 ('771 patent). Hypotensive compounds reduce blood pressure, like antihypertensives. Trial Tr. 781:4-9 (Ellis); 951:13-14 (Goldstein).

262. The '771 patent teaches that trazodone can be administered orally for the treatment of male sexual impotence and that the oral route is preferred: "Administration of

trazodone according to the present invention may be made by the parenteral, oral, or rectal routes. The oral route is preferred, however." DX 2189 at 4:52-54 ('771 patent).

263. Claim 2 of the '771 patent, which depends from claim 1 of the '771 patent, claims oral administration of trazodone for the treatment of male sexual impotence. DX 2189, claim 2 ('771 patent).

264. U.S. Patent No. 5,177,070 ("the '070 patent") is titled: "Method Of Treating Physiologic Male Erectile Impotence." DX 2190 ('070 patent). It issued on January 5, 1993. DX 2190 ('070 patent). It is prior art to the '012 patent and would have been available to the POSA.

265. The abstract of the '070 patent states: "Method of treating male erectile impotence secondary to physiological dysfunction by administering, preferably orally, the cholinergic agent galanthamine." DX 2190 ('070 patent).

266. The '070 patent teaches the use of galanthamine for the treatment of male sexual impotence: "The present invention is a method of treating non-psychogenic forms of male erectile impotence in a male animal in need of such treatment comprising administering to such male animal an erectile impotence treating therapeutically effective amount of galanthamine." DX 2190 at 2:29-33 ('070 patent).

267. The '070 patent teaches that the preferred route of administration is oral: "The dosage unit is most advantageously tablets or capsules, but may be any other convenient dosage form. While the preferable route of administration is oral, any other convenient mode of administration may be used." DX 2190 at 2:50-54.

268. The '070 patent provides an example of oral administration to a male human to treat ED: "A human male patient suffering from a senile loss of erectile function in conjunction

with normal aging and its sequelae is given 20 mg of galanthamine hydrobromide orally three times a day to alleviate erectile dysfunction." DX 2190 at 3:23-29.

C. A POSA Would Have Been Aware Of Potent And Selective PDE5 Inhibitors, Including Sildenafil

269. By June 9, 1993, the compounds identified for use in the method of the asserted claims, including sildenafil, had been publicly disclosed as potent and selective inhibitors of PDE5 in Pfizer's European Patent Application Publication No. 0463756A1 ("EP '756") (DX 2074 at 3:1-2) and European Patent Application Publication No. 0526004 A1 ("EP '004") (DX 2006 at 2:1-2). A POSA would have known about those published applications. Trial Tr. 322:20–323:20 (Corbin).

270. A POSA also would have known of the compound zaprinast and the fact that zaprinast selectively inhibited PDE5, and is one to two orders of magnitude more potent for inhibiting PDE5 than PDE1. *See* DX 2138A at 152, Table III (Murray 1993); Trial Tr. 149:23-152:6 (Corbin).

1. EP '756 Disclosed Potent and Selective PDE5 Inhibitors, Including Sildenafil

271. EP '756, titled "Pyrazolopyrimidinone Antianginal Agents," was published on January 2, 1992. DX 2074 (EP '756).

272. EP '756 discloses compounds that are potent and selective inhibitors of cGMP PDE and have utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis. DX 2074 at 1:1-14 (EP '756).

273. EP '756 discloses seven especially preferred compounds:

5-[2-allyloxy-5-(4-methylpiperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimdin-7-one;
5-[2-ethoxy-5-(piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;
5-[2-ethoxy-5-(4-methylpiperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-propyl)piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-hydroxyethyl)piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimdin-7-one;
1-methyl-5-[5-piperazinylsulphonyl)-2-n-propoxyphenyl]-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;
and 5-{5-[4-(2-hydroxyethyl)piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

DX 2074 at 4:16-19 (EP '756).

274. The third especially preferred compound is sildenafil. DX 2074 at 4:20-21 (EP '756). Sildenafil is also disclosed in EP '756 as Example 12. DX 2074 at 10 (EP '756); Trial Tr. 220:17-21 (Carson).

275. Five of the especially preferred compounds disclosed in EP '756 are compounds recited for use in the method of claim 25 of the '012 patent:

EP '756 Especially Preferred Compound	Corresponding Compound In Claim 25 Of the '012 Patent
3 (sildenafil)	3
1	4
4	5
5	6
7	7

Compare DX 2001 at 3:64-4:23 ('012 patent) to DX 2074 at 4:15-29 (EP '756); Trial Tr. 326:13–329:6 (Corbin).

276. EP '756 teaches that the disclosed compounds exhibit selectivity for inhibition of cGMP PDEs rather than cAMP PDEs. DX 2074 at 3:5-6 (EP '756); Trial Tr. 220:22-221:6 (Carson). A POSA would have understood that to mean that the compounds are selective inhibitors of PDE5 and PDE1. Trial Tr. 275:8-10 (Carson), 324:20–325:24 (Corbin).

277. EP ‘756 further teaches that as a consequence of their selectivity for inhibition of cGMP PDEs rather than cAMP PDEs, the disclosed compounds elevate cGMP levels, have beneficial vasodilatory activity, and potentiate the effects of EDRF and nitrovasodilators:

> as a consequence of this selective PDE inhibition, cGMP levels are elevated, which in turn can give rise to beneficial platelet anti-aggregatory, anti-vasospastic and vasodilatory activity, as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF) and nitrovasodilators. Thus the compounds have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

DX 2074 at 3:6-14 (EP ‘756).

278. EP ‘756 further discloses PDE activity studies, the results of which “show that the compounds of the present invention are potent and selective inhibitors of both cGMP PDEs.” DX 2074 at 6:56–7:8 (EP ‘756). A POSA would have known that the reference to the compounds as potent and selective inhibitors of “both cGMP PDEs” is a reference to selective inhibition of (1) PDE5, which is specific for cGMP as a substrate, and (2) PDE1, which can break down both cGMP and cAMP as a substrate. Trial Tr. 275:8-10 (Carson).

279. EP ‘756 further teaches that the disclosed compounds may be administered orally, in a range of 4-800 mg/day, in single or multiple doses, once or several times per day:

> For administration to man in the curative or prophylactic treatment of angina, hypertension or congestive heart failure, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day.

DX 2074 at 7:23-32 (EP '756).

280. In summary, EP '756 discloses sildenafil and other especially preferred compounds that are potent and selective PDE5 inhibitors, and discloses the oral administration, of those compounds at a range of 4-800 mg per day, one or more times per day, for the treatment of conditions that may be helped by a compound that elevates levels of cGMP and potentiates the effects of EDRF. DX 2074 at 3:6-14, 4:16-29, 7:23-32, 10 (Ex. 12) (EP '756).

2. **The '534 Patent (DX 2004) And The Ellis 1992 Declaration (DX 2240)**

281. Pfizer's U.S. Patent No. 5,250,534 ("the '534 patent"), titled "Pyrazolopyrimidinone Antianginal Agents," issued on October 5, 1993 from U.S. Patent Application Serial No. 07/882,988, which is a continuation of U.S. Patent Application Serial No. 07/717,227, filed June 18, 1991, now abandoned, and claims the benefit of the filing date of British Patent Application No. 9013750, filed June 20, 1990. DX 2004 ('534 patent).

282. The '534 patent names Andrew S. Bell, David Brown and Nicholas K. Terrett as co-inventors. DX 2004 ('534 patent).

283. The '534 patent is the United States counterpart to EP '756, and its specification is substantially identical to that of EP '756. DX 2004 ('534 patent); compare DX 2004 ('534 patent) and DX 2074 (EP '756).

284. The '534 patent discloses compounds that are potent and selective inhibitors of cGMP PDE and have utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis. DX 2004 at 1:13-38 ('534 patent).

285. The '534 patent discloses seven especially preferred compounds:

5-[2-allyloxy-5-(4-methylpiperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methylpiperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-propyl)piperazinylsulphonyl]-phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-hydroxyethyl)piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-methyl-5-[5-piperazinylsulphonyl)-2-n-propoxy-phenyl]-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and
5-{5-[4-(2-hydroxyethyl)piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

DX 2004 at 2:64–3:18 (‘534 patent).

286. The third especially preferred compound is sildenafil. DX 2004 at 3:4-6 (‘534 patent); Trial Tr. 220:17-21 (Carson).

287. The ‘534 patent also disclosed sildenafil as Example 12. DX 2004 at 10:1-35 (‘534 patent); Trial Tr. 331:3-13 (Corbin).

288. Five of the especially preferred compounds disclosed in the ‘534 patent are compounds recited for use in the method of claim 25 of the ‘012 patent:

‘534 Patent Especially Preferred Compound	Corresponding Compound In Claim 25 Of the ‘012 Patent
3 (sildenafil)	3
1	4
4	5
5	6
7	7

Compare DX 2001 at 3:64-4:23 (‘012 patent) and DX 2004 at 2:63-3:18 (‘534 patent).

289. The ‘534 patent teaches that the disclosed compounds may be administered orally, in a range of 4-800 mg/day, in single or multiple doses, once or several times per day:

> For administration to man in the curative or prophylactic treatment of angina, hypertension or congestive heart failure, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg). Thus for a typical adult

> patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day.

DX 2004 at 6:41-59 ('534 patent).

290. The '534 patent teaches that the disclosed compounds exhibit selectivity for inhibition of cGMP PDEs rather than cAMP PDEs and, as a consequence of this selective PDE inhibition, cGMP levels are elevated, which in turn can give rise to beneficial vasodilatory activity and potentiate the effects of EDRF and nitrovasodilators. DX 2004 at 1:20-28 ('534 patent).

291. The '534 patent teaches that the disclosed compounds have utility in the treatment of a number of disorders, including angina, hypertension, congestive heart failure and atherosclerosis. DX 2004 at 1:13-19, 1:28-39 ('534 patent).

292. During the prosecution of the application for the '534 patent, the applicants submitted a March 23, 1992 Declaration of Peter Ellis ("the Ellis 1992 Declaration"). DX 2240 (Ellis 1992 Declaration).

293. The Ellis 1992 Declaration contains a table titled: "In Vitro PDE Inhibitory Data: Selectivity Between Calcium/Calmodulin (Ca/CAM)-Independent cGMP PDE and cGMP-Inhibited cAMP PDE." DX 2240 at 4 (Table) (Ellis 1992 Declaration). That table discloses *in vitro* PDE inhibitory data for 20 of the compounds disclosed in the '534 patent (and EP '756). DX 2240 at 4 (Table) (Ellis 1992 Declaration). The twenty examples in the upper part of the Table, examples 9 to 58, are the compounds of the '534 patent. DX 2240 at 2 (¶ 4). Example 12 is sildenafil. DX 2240 at 4 (Table) (Ellis 1992 Declaration); Trial Tr. 331:3-13 (Corbin).

294. The Ellis 1992 Declaration states:

> [in the table,] inhibition of calcium/calmodulin (Ca/CAM)-independent cGMP PDE is compared with inhibition of cGMP-inhibited cAMP PDE, the selectivity ratio being the ratio of the latter values over the former values. The enzyme inhibitory activities are expressed either as IC_{50} values in nanomoles or as activities at 10^{-4} molar. It should be noted that the lower the number is, the more potent is the inhibitory activity of the compound. By contrast, in the selectivity ratio column, the higher the number is, the more selective is the compound in its PDE inhibitory profile.

DX 2240 at 2 (¶ 3) (Ellis 1992 Declaration).

295. A POSA would have understood "calcium/calmodulin (Ca/CAM)-independent cGMP PDE" to mean PDE5, and "cGMP-inhibited cAMP PDE" to mean PDE3. Trial Tr. 332:1-14 (Corbin). The table in the Ellis 1992 Declaration therefore discloses a POSA to disclose *in vitro* inhibitory activity against PDE5 and PDE3 for 20 of the compounds disclosed in the '534 patent (and EP '756), and each compound's selectivity for inhibition of PDE5 over PDE3. Trial Tr. 332:17-25 (Corbin), 1007:3-15 (Terrett).

296. The table in the Ellis 1992 Declaration discloses the following inhibitory data for sildenafil:

Example	IC_{50} (nM) or % activity at 10^{-4} M		Selectivity Ratio
	cGMP	cAMP	
12 (sildenafil)	3.6	65,000	18,056

DX 2240 at 4 (Table) (Ellis 1992 Declaration).

297. A POSA would have understood that the IC_{50} value in the column labeled cGMP represents the referenced compound's IC_{50} for the inhibition of PDE5. Trial Tr. 332:1-8 (Corbin). A POSA would have understood that the IC_{50} value in the column labeled cAMP represents the referenced compound's IC_{50} value for the inhibition of PDE3. Trial Tr. 332:9-16 (Corbin).

298. The IC_{50} data in the table of the Ellis 1992 Declaration to mean that the 20 tested compounds, including sildenafil, are highly potent inhibitors of PDE5, have little to no potency for inhibition of PDE3, and are highly selective for inhibition of PDE5 over PDE3. Trial Tr. 332:17-25 (Corbin).

299. A POSA would have recognized from the IC_{50} data in the Ellis 1992 Declaration that most of the 20 tested compounds, including sildenafil and the other especially preferred compounds, are about 100 times more potent against PDE5 than zaprinast. Trial Tr. 333:1-4 (Corbin).

300. The table of data in the Ellis 1992 Declaration became publicly available upon issuance of the '534 patent on October 5, 1993. DX 2004 ('534 patent).

301. The '534 patent is prior art to the '012 patent. DX 2004 ('534 patent).

302. The table of data in the Ellis 1992 Declaration is prior art to the '012 patent because on the day the '534 patent issued the Ellis 1992 Declaration became available to the public. DX 2004 ('534 patent).

3. **EP '004 (DX 2006)**

303. Pfizer's European Patent Application Publication No. 0526004 A1 ("EP '004"), titled "Pyrazolopyrimidinone Antianginal Agents," was published on February 3, 1993. DX 2006 (EP '004).

304. EP '004 discloses compounds that are potent and selective inhibitors of cGMP PDE and have utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis. DX 2006 at 2:1-14 (EP '004); Trial Tr. 333:19–334:7 (Corbin).

305. EP '004 discloses the following five especially preferred compounds:

5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-mehyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[5-(4-acetyl-1-piperazinyl)acetyl-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and 5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3- d]pyrimidin-7-one.

DX 2006 at 3:25-34 (EP '004); Trial Tr. 335:4-8 (Corbin).

306. Four of the especially preferred compounds disclosed in EP '004 are compounds recited for use in the method of claim 25 of the '012 patent:

EP '004 Especially Preferred Compound	Corresponding Compound In Claim 25 Of the '012 Patent
4	1
5	2
2	8
1	9

Compare DX 2001 at 3:64-4:23 ('012 patent) and DX 2006 at 3:25-34 (EP '004); Trial Tr. 335:13-25 (Corbin).

307. EP '004 teaches that the disclosed compounds may be administered orally, in a range of 4-800 mg/day, in single or multiple doses, once or several times per day:

> For administration to man in the curative or prophylactic treatment of angina, hypertension or congestive heart failure, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day.

DX 2006 at 9:11-15 (EP '004).

308. EP '004 contains a table titled: "In Vitro PDE Inhibitory Data: Selectivity Between Calcium/Calmodulin (Ca/CAM)-Independent cGMP PDE and cGMP-Inhibited cAMP PDE." DX 2006 at 26:1-35 (EP '004). That table discloses *in vitro* PDE inhibitory data for 13

of the compounds disclosed in EP '004. DX 2006 at 26:1-35 (EP '004); Trial Tr. 336:1-10 (Corbin). Those 13 compounds include the especially preferred compounds of EP '004. DX 2006 (EP '004).

309. A POSA would have understood "calcium/calmodulin (Ca/CAM)-independent cGMP PDE" to mean PDE5 (Trial Tr. 336:11-13 (Corbin)), and "cGMP-inhibited cAMP PDE" to mean PDE3. Trial Tr. 336:14-15 (Corbin). A POSA therefore would have understood the table in EP '004 to disclose *in vitro* inhibitory activity against PDE5 and PDE3 for 13 of the compounds disclosed in EP '004, and each compound's selectivity for PDE5 over PDE3. Trial Tr. 336:16-23 (Corbin).

310. The table in EP '004 discloses the following inhibitory data:

EXAMPLE	IC_{50} (nM)		SELECTIVITY RATIO
	cGMP	cAMP	
3	2.2	86,000	39,090
4	1.8	63,000	35,000
11	4.9	57,000	11,632
14	1.0	57,000	57,000
15	3.4	75,000	22,058
16	3.7	53,000	14,324
20	3.7	59,000	15,945
25	3.4	84,000	24,705
29	5.5	84,000	15,272
30	1.4	58,000	41,428
31	3.4	56,000	16,470
32	1.4	38,000	27,142
39	5.3	54,000	10,188

DX 2006 at 26:1-35 (Table) (EP '004).

311. A POSA would have interpreted the IC_{50} value in the column labeled cGMP to mean the example compound's IC_{50} value for inhibition of PDE5. Trial Tr. 336:11-23 (Corbin).

A POSA would have interpreted the IC_{50} value in the column labeled cAMP to mean the example compound's IC_{50} value for inhibition of PDE3. Trial Tr. 336:11-23 (Corbin).

312. A POSA would have understood the IC_{50} data in the table of EP '004 to mean that the thirteen tested compounds, including the especially preferred compounds, are highly potent inhibitors PDE5, weak inhibitors of PDE3 and, consequently, highly selective for inhibition of PDE5 over inhibition of PDE3. Trial Tr. 336:19–337:15 (Corbin).

313. A POSA would have recognized from the data in the table of EP '004 that the especially preferred compounds are about 100 times more potent against PDE5 than zaprinast. Trial Tr. 336:24–337:2 (Corbin).

314. EP '004 also discloses the following information regarding animal toxicity studies conducted with the compounds of EP '004:

> Certain compounds of the invention have been tested at therapeutic doses of up to 1 mg/Kg i.v. and up to 3 mg/Kg p.o. in rats with no signs of adverse acute toxicity being observed. In mice, no deaths occurred after doses of up to 100 mg/Kg i.v.

DX 2006 at 26:37-41 (EP '004).

VII. THE PATENT-IN-SUIT (DX 2001)

315. The '012 patent issued on October 22, 2002 from the '792 application. The '792 application was filed as a U.S. national stage of PCT '580. DX 2001 ('012 patent). PCT '580 was filed on May 13, 1994. The '012 patent claims the benefit of the June 9, 1993 filing date of GB '920. DX 2001 ('012 patent).

A. GB '920 (DX 2007)

316. The subject-matter of GB '920 relates, among other things, to treating ED with any of a series of compounds that were previously disclosed in EP '756 and EP '004. DX 2007 at 2 (GB '920); *see* Trial Tr. 352:1-10 (Corbin).

317. GB '920 indicates that the compounds for use in the method of the "invention" are potent inhibitors of cGMP PDEs in contrast to cAMP PDEs. DX 2007 at 2 (GB '920).

318. GB '920 states that "selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the said compounds in EP-A-0463756 and EP-A-0526004." DX 2007 at 2 (GB '920).

319. Those utilities include the treatment of various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis. DX 2007 at 2 (GB '920).

320. GB '920 states: "It has now been found that these disclosed compounds are useful in the treatment of erectile dysfunction." DX 2007 at 2 (GB '920).

321. GB '920 states: "Furthermore the compounds may be administered orally, thereby obviating the disadvantages associated with i.c. [intracavernosal] administration." DX 2007 at 2 (GB '920).

322. GB '920 discloses the following nine especially preferred compounds:

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

DX 2007 at 6-7 (GB '920).

323. Sildenafil is the third compound in the list of nine especially preferred compounds in GB '920: 5-[2-ethoxy-5-(4-methylpiperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1 ,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one. DX 2007 at 6 (GB '920).

324. GB '920 states that the disclosed compounds are described in EP '756 and EP '004, that the methods for determining the cGMP PDE and cAMP PDE inhibitory activities of those compounds are described in EP '756 and EP '004, and that the routes of administration of those compounds for human use are described in EP '756 and EP '004.

> The compounds of formula (I) and their pharmaceutically acceptable salts, processes for the preparation thereof, in vitro test methods for determining the cGMP PDE and cAMP PDE inhibitory activities thereof, and the pharmaceutical compositions thereof and routes of administration for human use, are described in EP-A-0463756 and EP-A-0526004.

DX 2007 at 7 (GB '920).

325. EP ‘756 and EP ‘004 disclose that the routes of administration of the disclosed compounds for human use include oral, intravenous, buccal and sublingual administrations. DX 2004 at 9:11-29 (EP ‘756); DX 2074 at 7:23-41 (EP ‘004).

326. GB ‘920 states:

> Generally, in man, oral administration of the compounds of the invention is the preferred route, being the most convenient and avoiding the disadvantages associated with i.c. administration. A preferred dosing regimen for a typical man is 5 to 75 mg of compound three times daily.

DX 2007 at 7 (GB ‘920).

327. GB ‘920 does not disclose any dosing regimen other than the preferred dosing regimen of “5 to 75 mg of compound three times daily.” *See* DX 2007 (GB ‘920); *See* Ellis Dep. Tr. at 158:7-13, 159:3-5.

328. GB ‘920 does not provide any data from *in vitro* or *in vivo* testing of any disclosed compound or any other data about any compound of formula (I). Trial Tr. 352:11–353:2 (Corbin); *see* DX 2007 (GB ‘920); Terrett Dep. Tr. at 115:16-21.

B. The ‘012 Patent (DX 2001)

329. The subject-matter of the ‘012 patent relates, among other things, to treating ED with prior art compounds known to be potent and selective cGMP PDE inhibitors. DX 2001 (‘012 patent).

1. Prosecution Of The Application For The ‘012 Patent

Prior Art Considered By The Examiner

330. During prosecution of the ‘792 application, the application which issued as the ‘012 patent, the Examiner rejected the claims as obvious over combinations of at least the following prior art references:

- Bowman *et al., Cyclic GMP Mediates Neurogenic Relaxation in the Bovine Retractor Penis Muscle,* 81 BR. J. PHARMACOL. 665–674 (1984) ("Bowman 1984") (DX 2269A)

- Bush 1992 (DX 2176A)

- Rajfer 1992 (DX 2109A)

- Murray 1993 (DX 2138A)

- EP '756 (DX 2074)

- EP '004 (DX 2006)

PTX 004 at PFZFH0010649–56 at 5 (Oct. 9, 1996 Office Action); PTX 4 at PFZFH0010719–26 at 3–4 (Aug. 12, 1997 Office Action).

The Applicants For The '012 Patent Submitted Evidence Of Allegedly Unexpected Results

331. On February 10, 1998, the applicants for the '012 patent submitted to the USPTO a Third Declaration Under 37 CFR 1.132 of Stephen A. Ballard ("Third Ballard Declaration"). PTX 4 at PFZFH0010860–72 (Third Ballard Declaration).

332. The Third Ballard Declaration compared PDE5 inhibitory activity of 83 compounds falling within the scope of the compounds recited for use in the claims of the application, with the PDE5 inhibitory activity of zaprinast. The Third Ballard Declaration provided the IC_{50} values for those 83 compounds and zaprinast in Table B. Numbers in that table shown in parentheses were for inhibition of PDE5 isolated from rabbit platelets, and numbers not in parentheses were for inhibition of PDE5 isolated from human corpus cavernosum. PTX 004 at PFZFH0010860–72 at ¶¶ 6-7, Appendix II (Third Ballard Declaration).

333. The Third Ballard Declaration states that "[a]ll compounds other than compound 8, 9 and 62 had IC_{50}s unexpectedly lower (at least a factor of five-fold) than that of zaprinast," and that "[t]he IC_{50} values shown in Table B unequivocally demonstrate that Applicants'

compounds as defined in claim 12 generally possess unexpectedly good PDEv inhibitory activity relative to zaprinast." PTX 4 at PFZFH0010860–72 at ¶ 7 (Third Ballard Declaration).

334. The applicants for the '012 patent argued to the USPTO in numerous filings that the data in the Third Ballard Declaration established that the compounds used in the application for the '012 patent have "unexpectedly" superior PDE5 inhibitory activity relative to zaprinast. DX 2179 (Feb. 3, 1998 Interview Summary); PTX 004 at PFZFH0010820–51 at 29–31 (Feb. 10, 1998 Response After Final Rejection); PTX 004 at PFZFH0010900–39 at 31 (Aug. 5, 1998 Brief for Appellants); PTX 004 at PFZFH0014393–420 at 18 (Dec. 26, 2001 Amendment).

335. The superior PDE5 inhibitory activity of the compounds used in the application for the '012 patent relative to zaprinast was not unexpected because the PDE5 IC_{50} value of zaprinast had been disclosed many times in the prior art (*see, e.g.*, DX-2138A at 152, 154, 155 (Murray 1993)), and because the PDE5 inhibitory data used in the application for the '012 patent, including claims 25 and 26 of the '012 patent, were disclosed in the prior art EP '004 (DX 2006 at 26 (EP '004)) or the Ellis 1992 Declaration (DX 2240 at Table, page 4(Ellis Declaration)).

336. The Third Ballard Declaration states: "I am aware of data obtained from screening assays which employ PDE_v isoenzyme isolated from rabbit platelet and rely on it as an accurate predictor of potency against human enzyme, although I was not involved in its generation." PTX 4 at PFZFH0010860–72 at ¶ 2 (Third Ballard Declaration).

337. Notwithstanding that the IC_{50} values for PDE5 inhibition of some of the compounds used in the '012 patent were disclosed in the prior art, the applicants for the '012 patent argued that the PDE5 potency data demonstrated unexpected results. PTX 004 at PFZFH0010820–51 at 29–31 (Feb. 10, 1998 Response After Final Rejection); PTX 004 at

PFZFH0010900–39 at 31 (Aug. 5, 1998 Brief for Appellants); PTX 004 at PFZFH0014393–420 at 18 (Dec. 26, 2001 Amendment).

338. The applicants for the ‘012 patent did not advise the USPTO that some of the “unexpected” PDE5 inhibitory activity data in the Third Ballard Declaration was disclosed in the prior art. Without that information, the USPTO found the evidence of unexpected results in the Third Ballard Declaration to be sufficient to overcome a number of obviousness rejections based upon combinations of Murray 1993, Bush 1992, Rajfer 1992, Bowman 1984, EP ‘756 and EP ‘004. PTX 004 at PFZFH0010891–94 (Apr. 22, 1998 Advisory Action), at 2; PTX 004 at PFZFH0002747–71 at 12–13 (Oct. 18, 1998 Examiner’s Answer); PTX 004 at PFZFH0015595–98 at 2 (Mar. 15, 2002 Office Action).

Allowance And Issuance

339. The ‘012 patent issued on October 22, 2002. DX 2001 (‘012 Patent).

340. That same day, Pfizer filed two complaints in the United States District Court for the District of Delaware seeking to enforce the ‘012 patent against Lilly ICOS *et al*. and Bayer AG *et al*. DX 2300 (Bayer Complaint); DX 2301 (Lilly Complaint).

2. **The Reexamination Of The ‘012 Patent**

341. The Director of the USPTO initiated a proceeding to reexamine the ‘012 patent on September 29, 2003, at which time the PTO reopened prosecution to examine the validity of claims 1–26 of the ‘012 patent. PTX 005 at PFZFH0026872–79 (Director Initiated Order for Reexamination).

342. The reexamination proceeding commenced by the USPTO was consolidated with three other reexaminations of the ‘012 patent commenced later at the request of third parties. *See* PTX 5 at PFZFH0102207–263 at 2–3 (BPAI Decision).

343. During reexamination of the ‘012 patent, the USPTO found there to be substantial new questions of patentability under 35 U.S.C. §§ 102 and/or 103 with respect to at least the following prior art references:

- Murray 1993 (DX 2138A)
- EP ‘756 (DX 2074)
- EP ‘004 (DX 2006)
- The ‘534 patent (DX 2004)

PTX 5 at PFZFH0051782–833 at 5 (Feb. 10, 2005 Office Action).

344. During reexamination of the ‘012 patent, the USPTO found there to be substantial new questions of patentability with respect to whether claim 24 is invalid for obviousness-type double patenting over, *inter alia*, Claim 1 of U.S. Patent No. 6,100,270 (“the ‘270 patent”) (DX 2066). PTX 5 at PFZFH0051782–833 at 6 (Feb. 10, 2005 Office Action).

345. On February 10, 2005, before the United States Supreme Court issued its opinion on the obviousness standard in *KSR*, 550 U.S. 398, the USPTO confirmed the patentability of, *inter alia*, claims 25 and 26 of the ‘012 patent, finding that those claims were not obvious over Murray 1993, EP ‘756, EP ‘004 and the ‘534 patent. PTX 5 at PFZFH0051782–833 (Feb. 10, 2005 Office Action).

346. In the February 10, 2005 office action, the Examiner stated:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant’s disclosure.

PTX 5 at PFZFH0051782–833 at 31 (Feb. 10, 2005 Office Action).

347. The Examiner found that none of Murray 1993, EP '756, EP '004 or the '534 patent, alone or combined, established a *prima facie* case of obviousness because the references did not contain a "direct teaching," or "specific guidance," or an "explicit suggestion or motivation" to use a selective PDE5 inhibitor to treat ED. PTX 5 at PFZFH0051782–833 at ¶¶ 7, 11, 65 (Feb. 10, 2005 Office Action).

348. On February 12, 2010, the Board of Patent Appeals and Interferences ("BPAI") found claim 24 unpatentable as anticipated under 35 U.S.C. § 102(a) and for obviousness-type double patenting over, *iter alia*, claim 1 of U.S. Patent No. 6,100,270 ("the '270 patent"). The BPAI found that claim 1 of the '270 patent qualified as double patenting references. DX 2303 at 47-53 (February 12, 2010 BPAI Decision).

349. During reexamination of the '012 patent, the USPTO did not consider whether any of claims 1–23, 25 or 26 were invalid for obviousness-type double patenting over claim 1 of the '270 patent. DX 2303 (February 12, 2010 BPAI Decision).

350. Pfizer canceled claim 24 of the '012 patent on March 26, 2010. PTX 5 at PFZFH0107812–18 (Mar. 26, 2010 Amendment).

351. The USPTO issued an Ex Parte Reexamination Certification on November 2, 2010. PTX 3 ('012 patent Reexamination Certificate).

3. The Subject Matter Of The '012 Patent

352. The compounds disclosed in the '012 patent for use in the claimed methods had previously been disclosed in EP '756 and EP '004 as potent and selective inhibitors of cGMP PDEs. DX 2001 at 1:46-61 ('012 patent); DX 2006 at 19-46 (EP '004); DX 2074 at 3:19-49 (EP '756); Trial Tr. 220:17-221:6 (Carson).

353. The ‘012 patent states that the selective inhibition of cGMP PDEs exhibited by those previously disclosed compounds provides the basis for their previously disclosed utilities:

> This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the said compounds in EP-A-0463756 and EP-A-0526004, namely in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

DX 2001 at 1:50-61 (‘012 patent).

354. The ‘012 patent discloses the use of a selective cGMP PDE5 inhibitor for the treatment of ED. DX 2001 at 1:46-50 (‘012 patent).

355. The ‘012 patent discloses the following nine especially preferred compounds for use in the method of the claimed “invention”:

> 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1, 6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
>
> 5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1, 6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
>
> 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one;
>
> 5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one;
>
> 5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinyl-sulphonyl] phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one;
>
> 5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
>
> 5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one; and
5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

DX 2001 at 3:64–4:23 ('012 patent).

356. The third especially preferred compound is sildenafil: 5-[2-ethoxy-5-(4-methylpiperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one. DX 2001 at 4:3-5 ('012 patent).

357. The nine especially preferred compounds of the '012 patent, all of which are claimed as compounds for use in the method of claim 25, were previously disclosed as especially preferred compounds in EP '756 and EP '004 as follows:

Compound For Use In The Method Of Claim 25	Corresponding Especially Preferred Compound In EP '756	Corresponding Especially Preferred Compound In EP '004
1		4
2		5
3	3	
4	1	
5	4	
6	5	
7	7	
8		2
9		1

Compare DX 2001 at 3:64-4:23 ('012 patent) to DX 2006 at 3:25-34 ('004 patent) and DX 2074 at 4:15-29 ('756 patent); Trial Tr. 326:13-329:11, 334:19-335:25 (Corbin).

358. The specification of the '012 patent does not identify sildenafil (or any other compound) as the most preferred compound. *See* DX 2001 ('012 patent).

359. The '012 patent discloses a study that demonstrated that human corpus cavernosum tissue contains three PDE isozymes, PDE2, PDE3 and PDE5 and that PDE5 is the predominant PDE isozyme. DX 2001 at 5:9-19 ('012 patent).

360. The ‘012 patent does not provide information about the relative amounts of PDE2, PDE3 and PDE5 present in the human corpus cavernosum. Ellis Dep. Tr. at 174:24-176:4.

361. GB ‘920 does not provide any disclosure regarding the isozymes present in the human corpus cavernosum. Trial Tr. 353:25–354:8 (Corbin); Ellis Dep. Tr. at 157:9-13.

362. By June 1993, it was known that PDE5 was present in the human corpus cavernosum. DX 2172A at Abstract 285 (Taher 1993); Trial Tr. 346:8-14 (Corbin).

363. By June 1993 it was known that PDE5 was the only cGMP PDE present in the human corpus cavernosum. DX 2172A at Abstract 285 (Taher 1993); Trial Tr. 346:8-16 (Corbin).

364. The ‘012 patent gives *in vitro* inhibition data for one of the especially preferred compounds, stating it has an inhibitory IC_{50} value of 6.8 nM when tested against PDE5 and has an IC_{50} of greater than 100 µM against PDE2 and has an IC_{50} of 34 µM against PDE3. DX 2001 at 5:36-40 (‘012 patent); Trial Tr. 344:22–345:1 (Corbin).

365. The ‘012 patent does not identify the compound used to generate the disclosed *in vitro* inhibitory data. Trial Tr. 344:22–345:8 (Corbin); Ellis Dep. Tr. at 199:13-17.

366. The IC_{50} data disclosed in the ‘012 patent for inhibition of PDE5 and PDE3 is in the same ballpark as the IC_{50} data disclosed in EP ‘004 and WO ‘104. DX 2006 at 26 (EP ‘004); DX 2068 at 18-19 (WO ‘104); Trial Tr. 345:9-12 (Corbin).

367. The ‘012 patent does not disclose the potency of the disclosed compounds for inhibition of PDE1. Trial Tr. 345:15-16 (Corbin), 282:24-283:19 (Carson).

368. A POSA could not tell from the disclosure of the ‘012 patent whether the compounds disclosed for use in the method of the ‘012 patent are more selective for inhibition of

PDE5 than they are for inhibition of PDE1. Trial Tr. 345:17-19 (Corbin), 282:24-283:19 (Carson).

369. GB '920 does not include any of those *in vitro* inhibition data. Trial Tr. 352:11-13 (Corbin); Ellis Dep. Tr. 157:18-158:6.

370. The *in-vitro* inhibitory activity of the especially preferred compounds of the '012 patent were disclosed in the prior art EP '004 publication and the Ellis 1992 Declaration. DX 2006 at 26 (EP '004); DX 2240 at 4 (Ellis Declaration).

371. The '012 patent discloses that oral administration is the preferred route of administration. DX 2001 at 5:62-65 ('012 patent). Other disclosed routes of administration include sublingual or buccal. DX 2001 at 5:66–6:3 ('012 patent).

372. Prior art patents had disclosed oral administration of other ED treatments, including vasodilating drugs, as a preferred route of administration that was effective and safe, and claimed oral administration of those drugs to treat ED. *See, e.g.*, DX 2191 at 2:60-67 ('449 patent); DX 2189 at 4:52-54, 6:6-7 (claim 2) ('771 patent).

373. The '012 patent discloses a preferred dosing regimen of 5 to 75 mg of compound three times a day. DX 2001 at 5:65-66 ('012 patent). The '012 patent does not disclose any other dosing regimen. *See* DX 2001 ('012 patent).

374. The prior art EP '756 and EP '004 publications had disclosed dosing regimens that encompassed administration of 5 to 75 mg of compound three times a day. DX 2006 at 9:11-13 (4-800mg/day)(EP '004); DX 2074 at 7:23-25 (4-800mg/day) (EP '756).

375. Sildenafil, one of the especially preferred compounds for use in the methods claimed in the '012 patent, is the active pharmaceutical ingredient in Pfizer's commercial Viagra® product for the treatment of ED. DX 2037 at 1 (Prescribing Information).

376. The Dosage and Administration section of the Viagra® Patient Prescribing Information states:

> For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, VIAGRA may be taken anywhere from 4 hours to 0.5 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day.

DX 2037 at 24 (Prescribing Information).

377. The '012 patent does not disclose once daily administration of sildenafil (or any other compound) for the treatment of ED. DX 2001 ('012 patent).

378. The '012 patent also does not disclose as needed administration of sildenafil (or any other compound) for the treatment of ED. DX 2001 ('012 patent).

379. The '012 patent does not disclose administration of sildenafil (or any other compound) at any specified amount of time before sexual activity, including 1 hour before sexual activity or 0.5 to 4 hours before sexual activity. DX 2001 ('012 patent).

380. The '012 patent does not disclose once daily oral administration of sildenafil (or any other compound) for the treatment of ED. DX 2001 ('012 patent).

381. The '012 patent discloses that volunteer and patient studies of some of the especially preferred compounds were conducted:

> In man, certain especially preferred compounds have been tested orally in both single dose and multiple dose volunteer studies. Moreover, patient studies conducted thus far have confirmed that one of the especially preferred compounds induces penile erection in impotent males.

DX 2001 at 5:52-56 ('012 patent).

382. A POSA would have understood that volunteer studies are conducted on healthy individuals, and that the "volunteer studies" mentioned in the '012 patent would not have been conducted on men with ED. Osterloh Dep. Tr. at 29:14-30:25; Ellis Dep. Tr. at 200:25-202:19.

383. The '012 patent specification does not provide any information about (1) which compounds were administered in the volunteer studies; (2) the results of the volunteer studies; (3) the dose frequency or amount administered in the volunteer studies; (4) the number of individuals who participated in the volunteer studies; or (5) whether any of the volunteers in the volunteer studies experienced erections. DX 2001 ('012 patent); Ellis Dep. Tr. at 202:24-203:9, 204:6-205:16, 206:19-207:12.

384. In the patient studies disclosed in the '012 patent, Pfizer administered at least one especially preferred compound to impotent men, and upon such administration at least some of those impotent men experienced erections. DX 2001 at 5:56-56 ('012 patent).

385. The '012 patent does not disclose the following with regard to the patient studies: (a) the severity or cause of the impotence in the males in the study; (b) which especially preferred compound induced erections in impotent males; (c) the route of administration (oral, buccal, parenteral, etc.); (d) the dosage administered; (e) the frequency of administration; (f) the timing of administration in relation to anticipated sexual activity; (g) how many individuals received the unnamed compound; (h) whether there was any sexual stimulation, and if so, what type; (i) the percentage of the patients that experienced erections; (j) how long the unnamed compound took to induce an erection; (k) whether the erection was sufficient for sexual intercourse; or (l) whether any especially preferred compound failed to induce erections in impotent males. *See* DX 2001 ('012 patent); Ellis Dep. Tr. 202:24-203:9, 204:6-205:5, 205:10-16, 207:2-12.

386. Claims 25 and 26 of the ‘012 patent do not have any limitations directed to side effects. DX 2001 at 10:1-39 (‘012 patent); Trial Tr. 228:1-17, 277:4-6 (Carson).

VIII. CLAIMS 25 AND 26 OF THE ‘012 PATENT ARE NOT ENTITLED TO A JUNE 9, 1993 PRIORITY DATE

387. Claims 25 and 26 of the ‘012 patent are directed to a method of treating ED by orally administering recited compounds, including sildenafil, to a male human in need of such treatment. DX 2001 at 10:1-39 (‘012 patent).

388. GB ‘920 does not disclose that any *in vitro* or *in vivo* testing was conducted using sildenafil or any other disclosed compound. DX 2007 (GB ‘920); Trial Tr. 352:11 353:2 (Corbin); *see* Ellis Dep. Tr. at 198:9-200:8.

389. GB ‘920 does not provide any data from any *in vitro* or *in vivo* testing of sildenafil or any other disclosed compound. DX 2007 (GB ‘920); Trial Tr. 352:11–353:2 (Corbin); *see* Ellis Dep. Tr. at 198:9-200:8.

390. GB ‘920 does not provide any other data for sildenafil or any other disclosed compound. DX 2007 (GB ‘920); Trial Tr. 352:11–353:2 (Corbin).

391. GB ‘920 does not provide any data or experimental proof that demonstrates that sildenafil or any other disclosed compound is effective to treat ED. DX 2007 (GB ‘920); Trial Tr. 353:3-6 (Corbin).

392. GB ‘920 does not provide any data or experimental proof that demonstrates that sildenafil or any other disclosed compound is safe to treat ED. DX 2007 (GB ‘920); Trial Tr. 353:7-10 (Corbin).

393. GB ‘920 does not provide any data or experimental proof that demonstrates that sildenafil or any other disclosed compound is effective to treat ED when orally administered. DX 2007 (GB ‘920); Trial Tr. 353:11-14 (Corbin).

394. GB ‘920 does not provide any data or experimental proof that demonstrates that sildenafil or any other disclosed compound is safe to treat ED when orally administered. DX 2007 (GB ‘920); Trial Tr. 353:15-18 (Corbin).

395. GB ‘920 does not indicate that sildenafil or any other disclosed compound had been shown to facilitate or cause erection when orally administered to a male human with ED. DX 2007 (GB ‘920); Trial Tr. 353:19-22 (Corbin).

396. GB ’920 does not disclose which PDE isoenzymes are present in the human corpus cavernosum. DX 2007 (GB ‘920); Trial Tr. 353:25–354:2 (Corbin); Ellis Dep. Tr. at 157:9-13.

397. GB ‘920 does not disclose which PDE isoenzyme in the corpus cavernosum is predominant. DX 2007 (GB ‘920); Trial Tr. 354:3-5 (Corbin); Ellis Dep. Tr. at 157:9-13.

398. GB ‘920 does not disclose the importance of PDE5 to the human erectile process. DX 2007 (GB ‘920); Trial Tr. 354:6-8 (Corbin); Ellis Dep. Tr. at 157:9-13.

399. GB ‘920 does not disclose any inhibitory data (or IC_{50} data) for sildenafil or any other disclosed compound. DX 2007 (GB ‘920); Trial Tr. 354:9-11 (Corbin); Ellis Dep. Tr. at 157:18-158:6.

400. GB ‘920 does not disclose any toxicity data for sildenafil or any other disclosed compound. DX 2007 (GB ‘920); Trial Tr. 354:12-14 (Corbin); Ellis Dep. Tr. at 157:14-17.

401. GB ‘920 does not disclose that sildenafil or any of the other disclosed compounds were administered orally in volunteer studies. DX 2007 (GB ‘920); Trial Tr. 354:15-18 (Corbin).

402. GB ‘920 does not disclose that sildenafil or any of the other disclosed compounds were used in volunteer studies. DX 2007 (GB ‘920); Trial Tr. 354:19-22 (Corbin).

403. GB ‘920 does not disclose that sildenafil or any of the other disclosed compounds were used in patient studies. DX 2007 (GB ‘920); Trial Tr. 354:23–355:1 (Corbin).

404. GB ‘920 does not disclose that sildenafil or any of the other especially preferred compounds induced penile erection in impotent males. DX 2007 (GB ‘920); Trial Tr. 354:23–355:1 (Corbin); Ellis Dep. Tr. at 159:22-160:2.

405. GB ‘920 does not provide any support for its statement that the compounds for use in the method of the alleged invention are effective in the treatment of ED when administered orally or otherwise. DX 2007 (GB ‘920); Trial Tr. 355:2-5 (Corbin).

406. GB ‘920 does not provide a POSA any basis for concluding that sildenafil or any other especially preferred compound could be administered orally to treat ED. DX 2007 (GB ‘920).

IX. CLAIMS 25 AND 26 OF THE ‘012 PATENT ARE OBVIOUS OVER RAJFER, MURRAY OR THE BUSH DISSERTATION IN VIEW OF EP ‘756, EP ‘004 AND THE GENERAL STATE OF THE ART

A. Claims 25 And 26 Of The ‘012 Patent

407. Claim 25 of the ‘012 patent is directed to a method of treating ED in a male human by orally administering an effective amount of one of nine recited compounds, including sildenafil, to a male human in need of such treatment. DX 2001 at 10:1-33 (‘012 patent).

408. Claim 26 depends from claim 25 and requires administration of sildenafil. DX 2001 at 10:34-39 (‘012 patent).

409. In light of the Court’s ruling on claim construction, claims 25 and 26 of the ‘012 patent have the following claim elements:

(a) oral administration;

(b) of a recited compound, such as sildenafil;

(c) to a male human in need of treatment for ED;

(d) in an amount sufficient to produce the desired effect; and

(e) for the purpose of treating ED.

DX 2001 at 10:1-39 (‘012 patent); Trial Tr. 359:2-8 (Corbin).

B. EP ‘756 And EP ‘004 Teach Every Element Of Claims 25 And 26 Of The ‘012 Patent Other Than Administration Of The Disclosed Compounds To A Male Human With ED For The Purpose Of Treating ED

410. EP ‘756 teaches every element of claims 25 and 26 of the ‘012 patent except the administration of the disclosed compounds to a male human with ED and for the purpose of treating ED. DX 2074 (EP ‘756); Trial Tr. 361:8-20 (Corbin).

411. EP ‘756 discloses sildenafil (claims 25 and 26) and four other compounds recited in claim 25 and teaches that sildenafil and those four other compounds are potent and selective PDE5 inhibitors that can be administered orally in a dosage range of 4-800 mg/day, in single or multiple doses, once or several times per day, to treat angina, hypertension or congestive heart failure. Trial Tr. 218:19-219:2 (Carson), 361:8-20 (Corbin).

412. EP ‘004 discloses four of the compounds recited in claim 25 (but not sildenafil) and teaches that those four compounds are potent and selective PDE5 inhibitors that can be administered orally in a dosage range of 4-800 mg/day, in single or multiple doses, once or several times per day, to treat angina, hypertension or congestive heart failure. Trial Tr. 333:12-335:23 (Corbin).

413. Each of the nine compounds recited in claim 25, including sildenafil, was disclosed in the prior art EP ‘756 or EP ‘004 publication. Compare DX 2001 at 10:1-39 (‘012 patent), DX 2006 at 3:25-34 (EP ‘004) and DX 2074 at 4:15-29 (EP ‘750); Trial Tr. 326:13-329:6, 333:12-335:23 (Corbin).

414. The Ellis 1992 Declaration and EP '004 also disclosed the IC_{50} values of the compounds recited in claim 25, including sildenafil, for inhibition of PDE5 and for inhibition of PDE3. DX 2006 at 26 (EP '004); DX 2240 at Table (Ex. 12) (Ellis Declaration); Trial Tr. 332:1-25, 336:1-337:15 (Corbin).

C. **The General State Of The Art**

415. By June 1993, a POSA would have believed that PDE3, PDE4 and PDE5 are present in the human corpus cavernosum. DX at 2172A at Abstract 285 (Taher 1993); Trial Tr. 155:10-18 (Corbin). A POSA would have recognized that PDE5 is the only cGMP PDE present in the human corpus cavernosum. Trial Tr. 155:10-21 (Corbin).

416. By June 1993, a POSA would have known that penile erection in male humans is caused by smooth muscle relaxation in the corpus cavernosum. Trial Tr. 119:9–120:1, 130:21-133:3, 143:14-22 (Corbin), 204:11–205:24 (Carson); DX 2109A at 90 (Rajfer 1992); DX 2165 at 8 (Bush Dissertation).

417. By June 1993, a POSA would have known that smooth muscle relaxation in the corpus cavernosum is mediated by the L-arginine-NO-cGMP pathway. *See supra* Section VI.A.2.

418. By June 1993, a POSA would have known that the L-arginine-NO-cGMP pathway in the corpus cavernosum is activated by stimulation of NANC neurons, and that sexual stimulation activates those NANC neurons. *See supra* Section VI.A.2.

419. By June 1993, a POSA would have understood the following aspects of the L-arginine-NO-cGMP pathway in the human corpus cavernosum:

(1) Upon stimulation of the NANC nerve, L-arginine releases NO;

(2) Nitric oxide penetrates corporal smooth muscle cells and activates guanylate cyclase;

(3) Guanylate cyclase catalyses the transformation of inactive GTP into active cGMP;

(4) Cyclic GMP signals protein kinase to cause cavernous smooth muscle relaxation, which leads to erection; and

(5) PDE5 regulates cGMP levels by catalyzing the degradation of cGMP into inactive 5'-GMP, a process which can be inhibited by PDE5 inhibitors such as zaprinast.

See supra Section VI.A.2; DX 2165 at 15-17 (Bush Dissertation); DX 2170A at 848 (Ignarro 1990); DX 2138A at 152 (Murray 1993); DX 2109A at 92 (Rajfer 1992); DX 2221A at 872, 875 (Trigo-Rocha II); DX 2172A at Abstract 285 (Taher 1993).

420. By June 1993, a POSA would have understood that a potent and selective PDE5 inhibitor would potentiate the effects of NO, leading to increased accumulation of cGMP, greater relaxation of cavernous smooth muscle and improved erectile function. Trial Tr. 226:15-227:16 (Carson).

421. By June 1993, a POSA would have been aware of selective PDE5 inhibitors such as zaprinast and the compounds disclosed in EP '756 and EP '004, including sildenafil. Trial Tr. 218:14-219:10 (Carson), 299:13-19, 300:25-301:13, 367:9-18 (Corbin), 556:19-24 (Bush).

D. Claims 25 And 26 Of The '012 Patent Are Prima Facie Obvious Over Rajfer 1992, Murray 1993 Or The Bush Dissertation In View Of EP '756, EP '004 And The General State Of The Art

422. As explained above, EP '756 discloses every element of claims 25 and 26 of the '012 patent except the administration of the disclosed compounds to a male human with ED for the purpose of treating ED.

423. As explained above, the POSA would have had a detailed understanding of the mechanism of erection, and the fact that a potent PDE5 inhibitor would potentiate erection. *See supra* Section IV.G.

1. **The Rajfer 1992 (DX 2109A)**

424. Rajfer 1992 reported that the PDE5 inhibitor zaprinast significantly enhanced relaxation of smooth muscle caused by either electrical stimulation or nitric oxide. DX 2109A at 92-93 (Rajfer 1992); Trial Tr. 296:20–297:19 (Corbin).

425. Rajfer 1992 stated that defects in the L-arginine-NO-cGMP pathway may cause some forms of impotence. DX 2109A at 94 (Rajfer 1992); Tr. 298:14–300:18, 300:25–301:13 (Corbin).

426. A POSA would have understood Rajfer to teach that compounds that potentiate the relaxation of the smooth muscle of the corpus cavernosum through the L-arginine-NO-cGMP pathway, such as selective PDE5 inhibitors, would be useful for the treatment of ED. Trial Tr. 299:13-19, 300:25–301:13 (Corbin); Terrett Dep. Tr. at 154:12-19, 155:10-11, 172:5-7, 172:11-16.

427. Rajfer 1992 disclosed every element of claim 25 and 26 of the ‘012 patent other than the use of the particular orally administrable cGMP PDE5 inhibitors recited for use in the methods of claims 25 and 26, including sildenafil. Trial Tr. 298:14–300:18, 300:25–301:13, 363:12-19 (Corbin).

2. **Murray 1993**

428. Murray 1993 teaches that selective PDE5 inhibitors should have therapeutic utility in treating ED. Trial Tr. 321:14-18 (Corbin); DX 2138A at 154-155 (Murray 1993). Murray 1993 bases that teaching on an understanding of the L-arginine-NO-cGMP pathway, PDE5’s role in regulating that pathway and Rajfer 1992’s disclosure that zaprinast, a selective PDE5 inhibitor, by itself caused a relaxation of human corpus cavernosum smooth muscle tissue and enhanced the relaxation caused by EFS or NO. DX 2138A at 152-153 (Murray 1993).

429. Murray 1993 explains that the combination of PDE5's limited tissue distribution in the body and its unique specificity for cGMP as a substrate suggests that a specific PDE5 inhibitor would have a narrow range of physiological and pharmacological actions. DX 2138A at 151 (Murray 1993); Trial Tr. 374:2–375:7 (Corbin).

430. Murray 1993 states that a PDE5 inhibitor could have selective action *in vivo* by virtue of the fact that many of the effects of PDE5 inhibitors in a particular tissue depend on the level of guanylate cyclase activity. DX 2138A at 155 (Murray 1993). A PDE5 inhibitor, therefore, will have the greatest effect in cells and tissues in which there is a high level of guanylate cyclase activity – *i.e.*, high levels of cGMP synthesis catalyzed by guanylate cyclase and, consequently, high levels of cGMP breakdown facilitated by PDE5. DX 2138A at 155 (Murray 1993); Trial Tr. 374:2-375:7 (Corbin).

431. Murray 1993 concludes that "a therapeutic agent that has little activity in its own right, but potentiates the effects of endogenous mediators" could have considerable value. DX 2138A at 155 (Murray 1993); Trial Tr. 376:4-18 (Corbin).

432. Sexual stimulation and the nitric oxide resulting therefrom are an endogenous mediator of cGMP synthesis. DX 2170 at 847-48 (Ignarro 1990); Trial Tr. 171:5-174:16, 374:2–375:7 (Corbin), 545:2-14, 546:1-5 (Bush).

433. Murray 1993 disclosed every element of claim 25 and 26 of the '012 patent other than the use of the particular orally administrable cGMP PDE5 inhibitors recited for use in the methods of claims 25 and 26, including sildenafil. *See supra* Section VI.A.3.(d).

3. **The Bush Dissertation (DX 2165)**

434. The Bush Dissertation teaches that a specific cGMP PDE inhibitor should enhance smooth muscle relaxation in the human corpus cavernosum and produce an erection by

having a direct and specific effect on the L-arginine-NO-cGMP mediated relaxation process by inhibiting the breakdown of cGMP. DX 2165 at 159-160 (Bush Dissertation).

435. The Bush Dissertation recommends the clinical development of a specific cGMP PDE inhibitor for the treatment of ED and suggests reevaluating any drugs that were being used to treat ED but whose mechanisms did not appear to have a physiological basis in the L-arginine-NO-cGMP pathway. DX 2165 at 160 (Bush Dissertation).

436. The Bush Dissertation disclosed every element of claim 25 and 26 of the ‘012 patent other than the use of the particular orally administrable cGMP PDE5 inhibitors recited for use in the methods of claims 25 and 26, including sildenafil. Trial Tr. 378:22–379:17 (Corbin).

4. A POSA Would Have Been Motivated To Use The Potent And Selective cGMP PDE Inhibitors Of EP ‘756 And EP ‘004 To Treat ED

437. Based on the teachings of Rajfer 1992, Murray 1993 or the Bush Dissertation in view of EP ‘756, EP ‘004 and the general state of the art, a POSA would have understood that a potent and selective PDE5 inhibitor such as sildenafil or any of the other especially preferred compounds of EP ‘756 or EP ‘004 would function in the L-arginine-NO-cGMP pathway to increase accumulation of cGMP, which was known to mediate smooth muscle relaxation in the corpus cavernosum and induce erection. Trial Tr. 359:23–361:2, 363:20–364:4 (Corbin); DX 2006 (EP ‘004); DX 2074 (EP ‘756).

438. A POSA would have had a reasonable expectation of success in treating ED in a male human by administering a potent and selective PDE5 inhibitor such as sildenafil (claims 25 and 26) or any of the other eight compounds recited in claim 25 of the ‘012 patent because zaprinast was known to facilitate smooth muscle relaxation, and the far more potent compounds disclosed in EP ‘756 and EP ‘004 would have been expected to facilitate smooth muscle

relaxation and the erections associated with such smooth muscle relaxation. Trial Tr. 359:23–361:2, 363:20–364:4 (Corbin).

439. A POSA would have been motivated to choose sildenafil or any of the other especially preferred compounds of EP '756 or EP '004 for treating ED because EP '756 and EP '004 indicate that sildenafil and the other especially preferred compounds are potent and selective cGMP PDE inhibitors, EP '004 provides potency and selectivity data, and the Ellis 1992 Declaration provides potency and selectivity data for sildenafil (claims 25 and 26) and four other compounds for use in the method of claim 25 of the '012 patent. Trial Tr. 359:23–361:2, 363:20–364:4 (Corbin); DX 2006 at 26 (EP '004), DX 2074 at 3:1-2 (EP '756); DX 2240 at Table (page 4) (Ellis Declaration).

5. A POSA Would Have Been Motivated To Orally Administer A Potent And Selective cGMP PDE Inhibitor Of EP '756 And EP '004 To Treat ED With A Reasonable Expectation Of Treating ED

440. A POSA would have been motivated to administer sildenafil or any of the other especially preferred compounds of EP '756 or EP '004 orally to treat ED in a male human. Trial Tr. 216:1-10, 219:5-10 (Carson), 367:9-18 (Corbin).

441. A POSA would have known that oral administration is the most convenient route of administration. Trial Tr. 216:1-10, 219:5-10 (Carson), 367:9-18 (Corbin).

442. A POSA reasonably would have expected that the oral administration of sildenafil or any of the other especially preferred compounds of EP '756 or EP '004 would be effective in targeting the erectile tissue in the penis because of PDE5's limited tissue distribution and its unique substrate specificity for cGMP. DX 2074 at 7:23-25 (EP '756); DX 2006 at 9:11-24 (EP '004), Trial Tr. 218:6-219:2, 219:25-220:11 (Carson), 367:19-368:10 (Corbin).

443. A POSA would have known of the teachings of Murray 1993 and would reasonably have expected that a potent and selective PDE5 inhibitor would have a narrow range

of physiological and pharmacological actions and would have its greatest effect in tissues in which there is a high level of guanylate cyclase activity, such as the corpus cavernosum. DX 2138A at 151, 155 (Murray 1993); Trial Tr. 316:23-318:18, 320:25-321:13 (Corbin).

444. EP '756 and EP '004 taught that sildenafil and the other especially preferred compounds of EP '756 and EP '004 could be administered orally in a dosage range of 4–800 mg daily, in single or multiple doses, once or several times per day. DX 2006 at 9:11-15 (EP '004); DX 2074 at 7:23-27 (EP '756).

445. A POSA would have known that the '445 and '771 patents taught orally administered vasodilators for the effective and safe treatment of ED, and taught that oral administration was a preferred route of administration. *See supra* ¶¶ 242-263. The '445 and '771 patents claimed oral administration of vasodilatory compounds for the treatment of ED. *See supra* ¶¶ 249, 263.

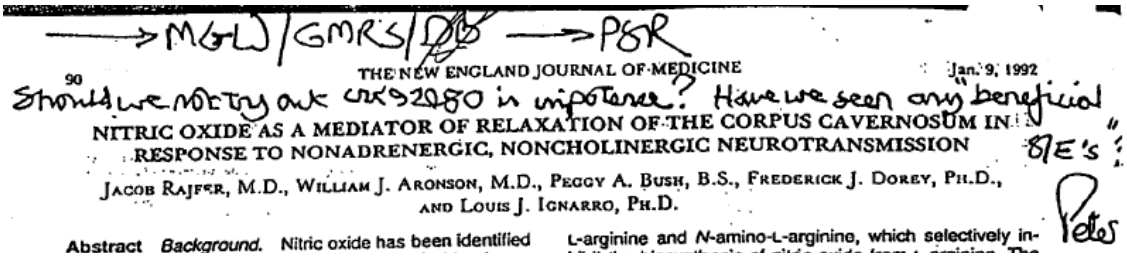
6. **Contemporaneous Evidence Supports Teva's Obviousness Arguments**

(a) In January 1992, Dr. Ringrose Understood Rajfer 1992 To Connect The Dots Between Sildenafil And Its Utility In The Treatment of ED

446. Individuals at Pfizer understood that Rajfer 1992 taught that selective PDE5 inhibitors, such as sildenafil, should have utility in treating impotence. Terrett Dep. Tr. at 185:09–187:24.

447. In January 1992, Dr. Peter Ringrose, then head of Pfizer Discovery, read Rajfer 1992 (DX 2109A) and circulated a copy of that article to the Pfizer Discovery group – which included Dr. Peter Ellis (a named co-inventor of the '012 patent) and several others involved in Pfizer's sildenafil development project. DX 2109 (Rajfer 1992); Ringrose Dep. Tr. at 122:03–126:07; s*ee* PTX 005 at PFZFH96536-96556 at PFZFH96546 (Ellis AU Aff.).

448. The copy of Rajfer 1992 that Dr. Ringrose circulated had the following note written at the top of the first page. "Should we not try out UK-92,480 [sildenafil] in impotence? Have we seen any beneficial S/E's [side effects]?" A copy of that note is reproduced below:


→ MGLJ/GMRS/DB → PSR

90 THE NEW ENGLAND JOURNAL OF MEDICINE Jan. 9, 1992

Should we not try out UK92480 in impotence? Have we seen any beneficial S/E's?

NITRIC OXIDE AS A MEDIATOR OF RELAXATION OF THE CORPUS CAVERNOSUM IN RESPONSE TO NONADRENERGIC, NONCHOLINERGIC NEUROTRANSMISSION

JACOB RAJFER, M.D., WILLIAM J. ARONSON, M.D., PEGGY A. BUSH, B.S., FREDERICK J. DOREY, PH.D., AND LOUIS J. IGNARRO, PH.D.

Abstract *Background.* Nitric oxide has been identified L-arginine and *N*-amino-L-arginine, which selectively in-

Pete's

DX 2109 (Ringrose Note); Ringrose Dep. Tr. at 122:03–123:23.

449. Dr. Ringrose understood Rajfer 1992 to connect the dots between the cGMP PDE-inhibiting compound sildenafil and its utility in the treatment of ED. Based on his understanding of the role of the L-arginine-NO-cGMP pathway in erection, as elucidated in Rajfer 1992, and based on his knowledge that sildenafil was a cGMP PDE inhibitor that could amplify cGMP levels, Dr. Ringrose believed that it would not be surprising for sildenafil to demonstrate utility in the treatment of ED. DX 2109 (Ringrose Note); Ringrose Dept. Tr. at 129:10–132:04; Terrett Dep. Tr. at 185:09–187:24.

450. Dr. Ringrose's note shows that Rajfer 1992 suggested to POSAs involved in the clinical development of selective PDE5 inhibitors to investigate whether those compounds have utility in the treatment of ED, and to reasonably expect them to have utility in the treatment of ED. DX 2109 (Ringrose Note); Terrett Dep. Tr. at 185:12–187:7.

451. Dr. Ellis received a copy of Rajfer 1992 bearing Dr. Ringrose's note several months before Pfizer first noted that volunteers in its Phase I clinical studies of sildenafil were reporting "spontaneous erections." DX 2109 (Ringrose Note); PTX 005 at PFZFH96536-96556 at PFZFH96546 (Ellis AU Aff.).

(b) In May 1993, Dr. Terrett Understood Murray 1993 To Teach That PDE5 Inhibitors Have Utility In The Treatment Of ED

452. Individuals at Pfizer understood that Murray 1993 taught that selective PDE5 inhibitors, such as sildenafil, should have utility in treating ED. DX 2136 (May 17, 1993 Terrett Memo); DX 2137 (May 26, 1993 Terrett Memo); DX 2108 at PFZ00706667 (July 1993 ECMT Memo); Terrett Dep. Tr. at 232:8-20.

453. Dr. Nicholas K. Terrett (a named co-inventor of the '012 patent) contemporaneously acknowledged that Murray 1993 confirmed that PDE5 inhibitors should have utility in treating ED. Terrett Dep. Tr. at 232:9-20.

454. On May 26, 1993, Dr. Terrett wrote an internal memorandum to Pfizer's sildenafil Early Candidate Management Team, in which he stated that, based on the comment in Murray 1993 that PDE5 inhibitors should have utility in treating ED, "this utility is no longer inventive." The paragraph from that memorandum containing those statements is reproduced below:

> **The critical role of NO in erection has been described in the literature, but until the last month there had been no specific reference to the possibility that cGMP PDEI's may have utility in impotence. Thus, we considered this utility to be novel and an inventive use of the compounds. Furthermore we assessed whether it may be possible to file a broad, 'field-of-use' claim for all cGMP PDEI's in impotence. However, a review has recently been published (Phosphodiesterase V_A Inhibitors, Murray, Drug News and Perspectives, 6 (3), April 1993, p150) that includes the comment that PDE V_A inhibitors could have utility in impotence. Therefore, this utility is no longer inventive, we are unable to file a 'field-of-use' claim for cGMP PDEI's, and we shall instead limit the patent to a second medical use of our compounds.**

DX 2137 (May 26, 1993 Terrett Memo).

455. The hypothesis set forth in Murray 1993 – *i.e.*, that a selective PDE5 inhibitor would have utility in the treatment of ED due to its effect on the cGMP pathway – was the identical hypothesis that Dr. Terrett and Dr. Ellis came up with for sildenafil's utility in the

treatment of ED. Terrett Dep. Tr. at 190:12-20, 232:21–234:17; DX 2108 at PFZ00706667 (July 1993 ECMT Memo).

456. Dr. Terrett's May 26, 1993 memorandum shows that a POSA would have understood Murray 1993 to teach that selective PDE5 inhibitors have utility in the treatment of ED.

(c) In December 1996, Pfizer Relied On Murray 1993 To Support Utility Of The Compound In Its Japanese Patent Application

457. One of Pfizer's Japanese counterparts of the '012 patent contained a claim that recited diseases on which the compounds of the alleged invention had effects. DX 2255 at 1 (Japanese App. Paper).

458. The Japanese Patent Office rejected that claim on the basis that it was not adequately supported by the specification, and invited Pfizer to submit prior art literature which explicitly taught, for example, a causal relationship between the PDE inhibition data and various diseases as stated in the specification. DX 2255 at 1 (Japanese App. Paper).

459. In a Written Argument dated December 3, 1996, Pfizer responded to the Japanese Patent Office rejection by citing Murray 1993, including its disclosure that a PDE5 inhibitor has potential therapeutic utilities including treatment of impotence, as providing "diseases for which a compound according to the present invention is highly plausibly effective." DX 2255 at 1-2 (Japanese App. Paper).

460. The Japanese Written Argument shows that Murray 1993 would have taught a POSA that it was "highly plausible" that a selective PDE5 inhibitor would have utility in the treatment of ED. DX 2255 at 2 (Japanese App. Paper).

(d) In The 1991–1992 Timeframe, Dr. Corbin Proposed Using Selective PDE5 Inhibitors For The Treatment Of ED

461. Dr. Jackie D. Corbin, a molecular physiologist and professor at Vanderbilt University, reasonably expected in the 1991–1992 timeframe that selective PDE5 inhibitors would have utility in treating ED. Trial Tr. 289:12-24 (Corbin).

462. After reading Ignarro 1990, Dr. Corbin realized that a selective inhibitor of PDE5 could be used to treat ED. Trial Tr. 174:21–176:6 (Corbin). Soon after that paper published, Dr. Corbin and his colleagues began to synthesize compounds that selectively inhibited PDE5. Trial Tr. 175:14–176:25 (Corbin).

463. Dr. Corbin discovered PDE5 in 1976, and in 1990 he and his colleagues became the first to purify PDE5. In the 1990–1993 timeframe, Dr. Corbin and his colleagues often referred to PDE5 as cGMP-binding phosphodiesterase, or cG-BPDE. DX 2276A (Thomas 1990).

464. On November 12, 1991, Dr. Corbin wrote a letter to Jackie Schrago of the Vanderbilt Department of Technology Transfer. DX 2275 (November 1991 Corbin Letter); Trial Tr. 177:2–178:16 (Corbin). In that letter, Dr. Corbin wrote that the cGMP analogs his group had synthesized and was attempting to patent should relax smooth muscle surrounding blood vessels and other tissues containing an important smooth muscle component. Dr. Corbin suggested that the cGMP analogs could be potentially beneficial to treat any malady that involves smooth muscle. DX 2275 (November 1991 Corbin Letter); Trial Tr. 177:2–178:2 (Corbin). Dr. Corbin stated: "Because smooth muscle relaxation is responsible for penile erections, male impotence could be treated by the analogs." DX 2275 (November 1991 Corbin Letter). Dr. Corbin further stated in that letter that the cGMP analogs could be used to "target most of the same diseases as a

class of drugs referred to as 'phosphodiesterase inhibitors[.]'" DX 2275 (November 1991 Corbin Letter); Trial Tr. 178:6-16 (Corbin).

465. On January 3, 1992, Dr. Corbin wrote a letter to Dr. Barry Ross of Glaxo Group Research Limited. DX 2455 (January 1992 Corbin Letter); Trial Tr. 178:17–179:15 (Corbin). In that letter, Dr. Corbin provided a general outline of his proposal for a collaborative Glaxo/Corbin research project. Dr. Corbin stated in that letter:

> It is well-known from the work of many groups, including our own, that the cG kinase has important disease-related functions other that the induction of vascular smooth muscle relaxation. Our cyclic GMP analogs and [PDE5] inhibitors should also work in these other systems. I mention here airway smooth muscle relaxation (asthma), corpus cavernosum relaxation (male impotence), and platelet aggregation inhibition (cardiovascular malfunction).

DX 2455 at 3 (January 1992 Corbin Letter); Trial Tr. 179:16–180:19, 181:18–182:10 (Corbin).

466. In January 1992, Dr. Corbin wrote a grant proposal for a collaborative Glaxo/Corbin research project, titled "Synthesizing cGMP Analogs and Phosphodiesterase Inhibitors to Prove the Mechanisms and Roles of Smooth Muscle Protein Kinases and Phosphodiesterases," to design and develop analogs of cGMP and PDE5 inhibitors. DX 2267 (Corbin Grant); Trial Tr. 182:11–183:8, 183:19–184:3 (Corbin). In that proposal, Dr. Corbin noted that "[PDE5] is present in high concentrations in vascular smooth muscle," and that since "[PDE5] regulates cyclic GMP levels in vascular smooth muscle, inhibitors of this enzyme should also be effective relaxants[.]" DX 2267 at 3 (Corbin Grant). Dr. Corbin mentioned that cGMP analogs and PDE5 inhibitors could be used for "corpus cavernosum relaxation" to treat "male impotence." DX 2267 at 1 (Corbin Grant); Trial Tr. 182:24–183:8 (Corbin).

467. In the proposal, Dr. Corbin proposed to "design PDE inhibitors based on the theory that the potency of existing inhibitors, such as IBMX and zaprinast, could be enhanced by

appending groups that would allow the inhibitors to more closely resemble the entire cyclic GMP molecule." DX 2267 at 3 (Corbin Grant); Trial Tr. 183:22–184:3 (Corbin).

468. Pfizer designed sildenafil using the structure of zaprinast as a chemical starting point. Terrett Dep. Tr. at 178:17–179:15 (Corbin).

469. Dr. Corbin realized in the 1991–1992 timeframe that PDE5 inhibitors should have utility in the treatment of ED. *See* Trial Tr. 174:21-176:6 (Corbin); DX 2267 at 3 (Corbin Grant); DX 2275 (November 1991 Corbin Letter); DX 2455 (January 1992 Corbin Letter).

7. Knowledge Regarding A Potential Nitric Oxide Defect In The L-Arginine-NO-cGMP Pathway Would Not Have Taught Away From The Use Of A Potent And Selective PDE5 Inhibitor For The Treatment Of ED

470. A POSA would not have been concerned that reduced production of nitric oxide in men with ED would prevent a potent and selective inhibitor of PDE5 from being able to treat ED because a POSA would not expect there to be zero nitric oxide and zero guanylate cyclase activity in men with ED, and because the synergistic effect of nitric oxide / cGMP production during sexual stimulation in combination with a potent and selective PDE5 inhibitor to prevent the break down of cGMP is a powerful effect and would result in a good elevation of cGMP. Trial Tr. 376:19-377:13 (Corbin).

471. There are different severities of ED. Dr. Goldstein worked with others to develop an Erection Hardness Scale (EHS) to measure the severity of ED. Trial Tr. 944:21-945:4 (Goldstein).

472. The EHS has four determinations or levels. A four on the EHS is a hard erection with no ED. Trial Tr. 945:21-945:7, 945:16-17 (Goldstein). A three on the EHS is a less hard erection than a four, but adequate for penetration. Trial Tr. 945:8-10 (Goldstein). A two on the EHS is less hard than a three and no longer adequate for penetration. Trial Tr. 945:11-13

(Goldstein). A one on the EHS is less hard than a two. It is not penetrable and is minimally hard. Trial Tr. 945:14-15 (Goldstein).

473. A male who scores a three on the erection hardness scale could have ED if he has other symptoms of ED. Trial Tr. 946:2-5 (Goldstein).

474. A POSA would expect that to the extent that nitric oxide production (or lack thereof) contributes to ED, a male with mild ED would have less of an issue with nitric oxide production than a male with severe ED.

475. A POSA would have known that a patient with mild ED might have less nitric oxide production that a patient without ED, but that there is still nitric oxide, and that use of a PDE5 inhibitor would decrease the breakdown of cGMP and actually increase the activity of the cGMP and facilitate erection. Trial Tr. 226:15-227:16 (Carson). The PDE5 inhibitor optimizes the nitric oxide present in the smooth muscle of the corpus cavernosum. Trial Tr. 226:15-227:16 (Carson).

476. A POSA would also know that during sexual stimulation there is continuous production of nitric oxide, resulting in increased levels of nitric oxide, and that even without sexual stimulation, there are basal levels of nitric oxide. Trial Tr. 227:17-25 (Carson).

477. Defects in nitric oxide production are only one possible cause of ED. Ellis Dep. Tr. 136:7-21. In those individuals in whom there would be no defect in the pathway then the cyclic GMP system would be intact. In those individuals in whom there was a defect in the pathway, whether enough nitric oxide is present would depend on the severity of the ED. Ellis Dep. Tr. 136:7-21.

8. Nitrovasodilators And PDE5 Inhibitors Impact cGMP Levels, But Do So Differently

478. A POSA would have understood that nitrovasodilators and PDE5 inhibitors both raise cGMP levels, but do so differently. Nitrovasodilators, such as nitroglycerin, donate or supply nitric oxide to the smooth muscle cells throughout the body, causing vasodilation throughout the body. Trial Tr. 225:15-226:3 (Carson). In contrast, during sexual stimulation, PDE5 inhibitors, which prevent PDE5 from metabolizing cGMP, have a greater impact on increasing cGMP levels in the penis than in the rest of the body, which results in greater smooth muscle relaxation in the penis than in the rest of the body, because sexual stimulation causes an increase in nitric oxide production and cGMP production in the penis but not in the rest of the body. Trial Tr. 224:5-226:3 (Carson).

E. Claims 25 And 26 Of The ‘012 Patent Are Prima Facie Obvious Over EP ‘756 Or The ‘534 Patent, In View Of The General State Of The Art

479. Claims 25 and 26 of the ‘012 patent are obvious over either EP ‘756 or the ‘534 patent in view of the general state of the art.

1. **EP ‘756 (DX 2074)**

480. EP ‘756 discloses seven especially preferred compounds, including sildenafil, and that sildenafil is a potent and selective inhibitor of cGMP PDE, including PDE5. DX 2074 at 1:1-4, 4:16-21, 10 (EP ‘756); Trial Tr. 327:23–328:22 (Corbin).

481. EP ‘756 discloses that sildenafil when administered orally has utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis when taken orally. DX 2074 at 3:6-14 (EP ‘756); Trial Tr. 218:14–219:10 (Carson).

482. EP ‘756 patent teaches that sildenafil may be administered orally, in a range of 4-800 mg/day, in single or multiple doses, once or several times per day in treating angina,

hypertension, heart failure and atherosclerosis. DX 2074 at 7:23-32 (EP '756); Trial Tr. 218:14–219:10.

483. The oral administration of sildenafil in the dosage range of 4-800 mg/day, in single or multiple doses, once or several times per day encompasses the preferred, and only, dosing region disclosed in the '012 patent. DX 2001 at 5:65-66 ('012 patent); Terrett Dep. at 160:3-10.

484. EP '756 teaches every element of claims 25 and 26 of the '012 patent except the administration of sildenafil to a male human with ED for the purpose of treating ED. DX 2074 (EP '756); Trial Tr. 361:8-20 (Corbin).

2. **The '534 Patent**

485. The '534 patent discloses seven especially preferred compounds, including sildenafil, and that sildenafil is a potent and selective inhibitor of cGMP PDE, including PDE5. DX 2004 at 2:57–3:19, 10:30-35 ('534 patent).

486. The '534 patent discloses that sildenafil when administered orally has utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis when taken orally. DX 2004 at 1:28-38 ('534 patent); Terrett Dep. Tr. at 48:8-12.

487. The '534 patent teaches that sildenafil may be administered orally, in a range of 4-800 mg/day, in single or multiple doses, once or several times per day in treating angina, hypertension, heart failure and atherosclerosis. DX 2004 at 6:41-56 ('534 patent).

488. The oral administration of sildenafil in the dosage range of 4-800 mg/day, in single or multiple doses, once or several times per day, would be effective in treating ED. DX 2001 at 5:65-66 ('012 patent); Terrett Dep. Tr. at 160:3-10.

489. The ‘534 patent teaches every element of claims 25 and 26 of the ‘012 patent except the administration of sildenafil to a male human with ED for the purpose of treating ED. DX 2004 at 2:57-3:19 (‘534 patent); Trial Tr. 330:24-331:13 (Corbin).

3. **The General State Of The Art**

490. A POSA would have known by June 9, 1993 that relaxation of the smooth muscle of the human corpus cavernosum is necessary for penile erection, that relaxation of the smooth muscle of the human corpus cavernosum and, consequently, penile erection, are mediated by the NANC neuron induced L-arginine-NO-cGMP pathway, that sexual stimulation triggers that pathway in man and that a selective PDE5 inhibitor would potentiate the effects of that pathway and therefore increase accumulation of cGMP in the corpus cavernosum, enhance relaxation of the smooth muscle in the corpus cavernosum and facilitate erection. *Supra* Section VI.A.

491. A POSA would have known by June 9, 1993 that ED has similarities with many of the cardiovascular disorders for which sildenafil was disclosed in EP ‘756 and the ‘534 patent to have therapeutic utility, including angina, hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease and stroke. Trial Tr. 218:14–219:10, 222:14–223:2 (Carson); Terrett Dep. Tr. at 153:25–154:21.

492. A POSA would have known by June 9, 1993 that spontaneous or unexpected erections are a rare side effect for drugs that are not being administered for the purpose of facilitating erections. Trial Tr. 764:21–765:3 (Ellis); Ellis Dep. Tr. at 146:8-147:17.

493. A POSA would have known that sildenafil was a potent and selective inhibitor of both PDE1 and PDE5. *Supra* Section VI.C; DX 2074 at 3:1-14; Trial Tri. 324:20-325:17, 334:16-18 (Corbin).

494. By June 9, 1993, a POSA would have known that PDE5 is present in the human corpus cavernosum, and that PDE1 is not present in the human corpus cavernosum. DX 2172A

at Abstract 285 (Taher 1993). A POSA would have recognized that PDE5 is the only cGMP PDE in the corpus cavernosum. DX 2171A (Taher 1992); DX 2172A at Abstract 285 (Taher 1993); Tr. 154:15-155:21, 346:8-16 (Corbin).

495. By May 13, 1994, a POSA would have known the potency of sildenafil for inhibition of PDE5 and PDE3, and selectivity of sildenafil for PDE5 over PDE3. *Supra* Section VI.C.

496. The Ellis 1992 Declaration discloses the following PDE inhibitory data for sildenafil:

Example	IC_{50} (nM) or % activity at 10^{-4} M		Selectivity Ratio
	cGMP	cAMP	
12 (sildenafil)	3.6	65,000	18,056

DX 2240 at 4 (Ellis Declaration).

497. A POSA would have understood the IC_{50} data in the table of the Ellis 1992 Declaration to mean that sildenafil is a highly potent inhibitor of PDE5, has little to no potency for inhibition of PDE3, and is highly selective for inhibition of PDE5 over PDE3. DX 2240 at 4 (Ellis Declaration); Trial Tr. 332:1–333:4 (Corbin).

498. A POSA would have understood that the side effect of erections should be investigated when treating patients orally with PDE5 inhibitors. DX 2109 (Ringrose Note); Terrett Dep. Tr. at 185:17–187:7; Ringrose Dep. Tr. at 137:23–138:9; Ellis Dep. Tr. at 146:8-147:17.

499. A POSA would have recognized sildenafil as the cause of spontaneous erections observed when administering sildenafil, a potent and selective PDE5 inhibitor, for the treatment of angina, hypertension, heart failure and atherosclerosis. Trial Tr. 700:19–701:3, 762:11–22, 765:4-11 (Ellis); Ringrose Dep. Tr. at 70:16–71:11; 75:5-13; Terrett Dep. Tr. at 40:16-21; Ellis Dep. Tr. at 126:24–127:3.

4. A POSA Would Have Been Motivated To Use Sildenafil Orally To Treat ED And Would Have Reasonably Expected It To Treat ED

500. The oral administration of sildenafil to a male human with ED in an amount effective to treat ED for the purpose of treating ED is obvious over the teachings of EP '756 or the '534 patent in view of the general state of the art.

501. EP '756 and the '534 patent teach a method of orally administering sildenafil, in a dosage range of 4-800 mg/day, in single or multiple doses, for the treatment of angina, hypertension or congestive heart failure. DX 2074 at 7:23-32 (EP '756); Trial Tr. 218:14–219:10 (Carson); DX 2004 at 6:41-56 (EP '534 patent).

502. Over a large portion of that dosage range, daily oral administration of sildenafil for the treatment of angina, hypertension or congestive heart failure, in single or multiple doses, would have resulted in a side effect of facilitated, spontaneous or unexpected erections in male humans who took any of the compounds disclosed in claims 25 and 26 of the '012 patent. DX 2001 at 5:65-66 ('012 patent); Trial Tr. 698:6–699:9, 700:19-702:3 (Ellis).

503. A POSA who practiced the methods disclosed in EP '756 or the '534 patent, or to whom the results of the practice of those methods was reported, would have recognized the side effect of facilitated, spontaneous or unexpected erections, and appreciated that the side effect was drug-related because: (1) erections are a rare side effect for drugs that are not being administered for the purpose of facilitating erections; and (2) the general state of the art was such that a POSA would have known that a selective PDE5 inhibitor such as sildenafil would inhibit the breakdown of cGMP by PDE5 in the corpus cavernosum, increase cGMP accumulation and thereby facilitate erection. Trial Tr. 698:6–699:9, 700:19–702:3, 762:11–765:11 (Ellis); DX 2109 (Ringrose Note); DX 2137 (May 26, 1993 Terrett Memo); DX 2138; Terrett Dep. Tr. at 47:2-6, 94:3-6, 185:9-187:24; Ellis Dep. Tr. at 146:5-147:17.

504. For the reasons set for above, a POSA who practiced the methods disclosed in EP ‘756 or the ‘534 patent, or to whom the results of the practice of those methods was reported, would have been motivated to orally administer sildenafil in a dosage range of 4-800 mg/day, in single or multiple doses, for the treatment of ED.

505. For the reasons set for above, a POSA who practiced the methods disclosed in EP ‘756 or the ‘534 patent, or to whom the results of the practice of those methods was reported, would reasonably have expected that orally administering sildenafil in a dosage range of 4-800 mg/day, in single or multiple doses, would be effective in the treatment of ED.

5. **Contemporaneous Evidence Supports Teva’s Obviousness Arguments**

506. In Pfizer’s Phase I clinical trials of sildenafil for use in treating angina, study volunteers received oral administrations of 25 mg, 50 mg or 75 mg of sildenafil three times per day. Numerous volunteers in those Phase I clinical trials reported spontaneous erections as a side effect after taking the drug. Ringrose Dep. Tr. at 70:16–71:11, 75:5-13; Terrett Dep. Tr. at 40:16-21; Ellis Dep. Tr. at 126:24–127:3.

507. Those reports of spontaneous erections led Pfizer to conclude that sildenafil might be useful for the treatment of ED as an orally administered drug. Ringrose Dep. Tr. at 70:16–71:11, 75:5-13; Terrett Dep. Tr. at 40:16-21; Ellis Dep. Tr. at 126:24–127:3.

508. A POSA would recognize that proerectile activity in healthy volunteers following the oral administration of sildenafil is a very strong marker that the oral administration of the compounds of EP ‘756 and the ‘012 patent would be useful for the treatment of ED. Ellis Dep. Tr. at 146:5-147:17.

509. A POSA who practiced the methods disclosed in EP ‘756 or the ‘534 patent encountering the side effect of spontaneous erections would have reached the same obvious conclusion as Pfizer reached. Ellis Dep. Tr. at 146:08-147:17.

F. Secondary Considerations Do Not Rebut Teva's Strong Case Of Prima Facie Obviousness

1. **There Is No Nexus Between The Sales And Profits Of Viagra® And Claims 25 And 26 Of The '012 Patent**

510. Any sales and profits for Viagra® are not indicative of the non-obviousness of claims 25 and 26 of the '012 patent because there is no nexus between the sales and profits of Viagra® and claims 25 and 26 of the '012 patent. Trial Tr. 600:5-9 (Hausman). There is no nexus because the compound known as sildenafil was under Pfizer's exclusive control due to Pfizer's ownership of the '534 patent (Trial Tr. 279:20-280:2 (Carson)), the sales and profits of Viagra® can be attributed to the '534 patent, oral administration for purposes of treating ED is not the claimed invention, Pfizer had a huge incentive to keep other PDE5 inhibitors off the market but failed, and pre-launch publicity cultivated by Pfizer, high levels of promotion by Pfizer at the time of launch and Pfizer's aggressive distribution plan for Viagra® contributed significantly to the sales and profits of Viagra® around the time of launch. Trial Tr. 600:13-16, 600:21-601:19 (Hausman).

(a) The '534 Patent Blocked Others From Practicing The Claimed Subject Matter Of The Asserted Claims

511. The '534 patent issued on October 5, 1993 from Application Serial No. 07/882,988 ("the '988 application"), filed on May 14, 1992. DX 2004 ('534 Patent); Trial Tr. 1037:1-6 (Grabowski). The '988 application is a continuation of Serial No. 07/717,227 ("the '227 application"), filed on June 18, 1991. DX 2004 ('534 Patent). The '534 patent claims the benefit of the filing date of Great Britain Application No. 9013750 ("GB '750"), filed on June 20, 1990. DX 2004 ('534 Patent).

512. Pfizer also owns a European patent on the compound known as sildenafil. The application for that patent published on January 2, 1992 as EP '756, which claims the benefit of

the filing date of GB ‘750 and contains a disclosure substantially identical to that of the ‘534 patent. DX 2074 (EP ‘756); Trial Tr. 602:10-16 (Hausman).

513. Pfizer synthesized sildenafil and other selective PDE5 inhibitors by 1990, ahead of the rest of the industry. Trial Tr. 603:4-22 (Hausman); DX 2302 at 2-4 (Ellis Canadian Declaration).

514. Pfizer’s control of the compound sildenafil and several uses of that compound were publicly disclosed with the publication of EP ‘756 on January 2, 1992. DX 2074 (EP ‘756); Trial Tr. 602:10-16 (Hausman).

515. Based on the publication of EP ‘756, a POSA would have known that sildenafil was under Pfizer’s exclusive control prior to the alleged invention claimed in the ‘012 patent. Trial Tr. 229:23-230:7, 279:20-280:2 (Carson), 603:23–604:6 (Hausman).

516. Economic analysis demonstrates the importance of Pfizer’s exclusive control of sildenafil. Trial Tr. 604:7–606:3, 617:12-24 (Hausman).

517. Much of the R&D in the pharmaceutical industry with respect to developing a new commercial product is a sunk and irreversible investment because the R&D is specific to a given drug and cannot be used to develop another drug or gain FDA approval for another drug. Thus, it would typically not make economic sense for a company, Company A, to develop a new drug when it knew that another company, Company B, owned a “blocking patent” on the drug. Trial Tr. 601:20–603:3, 604:19–606:13 (Hausman).

518. If Company A was successful, the blocking patent owner (Company B) could “hold up” Company A and extract the majority of the value of the new drug because of its blocking patent. Trial Tr. 601:20–602:9, 605:11–606:3 (Hausman); DX 2308 at 137-39 (Milgrom 1992).

519. Pfizer, which had the right under the '534 patent to exclude all others from using sildenafil (subject to the research exemption), would, with a very high probability, be the only company willing to do research on uses for the compound sildenafil. Trial Tr. 602:10–603:3 (Hausman).

520. Given the economic factor of sunk and irreversible investment in much of R&D to develop new drugs and the economic importance of the hold-up problem, it would be very unlikely for any other company to invest in research for any uses of the compound sildenafil. Trial Tr. 602:10–603:3, 605:11–606:3 (Hausman).

521. It also is highly unlikely that a company other than Pfizer would rely on the research exemption to investigate uses of compounds covered by the '534 patent and enter into an agreement with Pfizer regarding those uses. Trial Tr. 602:10–603:3 (Hausman). The few examples offered by Pfizer are situations in which a non-profit organization developed a use of an already-patented compound. Trial Tr. 1041:16-1044:23 (Grabowski). Such an agreement would be unlikely because Pfizer had the ability to design around the method patent obtained by the other company by using one of Pfizer's back-up compounds. Trial Tr. 606:4–608:2 (Hausman).

522. If the other company performed research and obtained a method patent for sildenafil, Pfizer could avoid the need for a license by developing a back-up compound discussed in the '534 and '012 patents. Trial Tr. 606:20–607:12 (Hausman), 1038:10-22 (Grabowski); Terrett Dep. Tr. at 49:18-22, 50:2-52:18, 56:19-57:9.

523. In that situation, the other company would be faced with earning no return on its substantial investment in research (because it could not sell sildenafil due to Pfizer's '534

patent), and thus the other company would have no incentive to perform the research in the first place. Trial Tr. 607:13-22, 633:24-634:3 (Hausman).

524. It would be very unlikely that a company would invest hundreds of millions of dollars in research if there would be a significant probability of earning no return because of Pfizer's '534 patent. Trial Tr. 607:20–608:2 (Hausman).

525. History shows that after one company obtains a patent directed to a compound a second, unrelated company rarely obtains a patent directed to a method of use of that compound. Occurrences of that type are quite rare and typically involve a second patent that is directed to an "improvement" of an existing drug. Trial Tr. 633:24-634:6, 636:18-637:9 (Hausman).

526. The preclusion of others in the market from developing uses for the compound sildenafil is a key fact leading to a conclusion that the sales and profits of Viagra® are at most a weak indicator of non-obviousness of the '012 patent. Trial Tr. 607:20-608:2 (Hausman).

(b) The Properties Of Sildenafil Are Claimed In The Earlier Issued '534 Patent

527. There is no nexus between the sales and profits of Viagra® and the method recited in claims 25 or 26 of the '012 patent. Trial Tr. 600:13-16, 600:21–601:19 (Hausman).

528. Claim 25 of the '012 patent claims a method of orally administering sildenafil and related compounds to a patient for the treatment of ED. Claim 26 is limited to a method of orally administering sildenafil. Trial Tr. 608:21-609:18 (Hausman).

529. The compound sildenafil is claimed in the '534 patent, a separate patent that is not at issue in this proceeding. If the sales of Viagra® have a nexus to any patent, it would be Pfizer's patent on the compound, not the '012 patent. Trial Tr. 604:7-606:12, 627:15-21 (Hausman).

530. Viagra®'s sales have been driven, in part by the substantial amount of promotion that Pfizer has directed toward Viagra®. *Infra* Section IX.F.1.(d).(ii).

531. It is the earlier-issued '534 patent directed to the compound sildenafil and the chemical properties of that compound that are associated with the sales and profits of Pfizer's Viagra®, not the claims of the '012 method patent at issue in this proceeding. Trial Tr. 604:7-18, 627:15-21 (Hausman).

532. Once the scientific evidence indicated that the chemical properties of PDE5 inhibitors such as sildenafil had a high probability of treating ED, the claims of the '012 patent directed to a method of treating ED by orally administering sildenafil or a related compound would have occurred if Pfizer did not have the right under the '534 patent to preclude all others from using the compound sildenafil. Trial Tr. 618:15-619:20, 630:20-631:21 (Hausman).

533. For example, in view of the knowledge in the art regarding the mechanism of erection, a POSA would reasonably have expected a selective PDE5 inhibitor, such as the compound sildenafil, to be effective for treating ED when orally administered, and to have targeted action in the human penis during sexual stimulation. Trial Tr. 618:15-619:20, 630:20-631:21 (Hausman).

534. It is the chemical properties of the compound sildenafil, *i.e.*, its selective inhibition of PDE5, and the effect of sildenafil on ED, that have led to the sales and profits associated with Viagra®. Trial Tr. 604:7-18, 627:15-21 (Hausman).

535. Demand for a successful treatment of ED was sufficiently high that the particular method claimed in claims 25 and 26 of the '012 patent had little or no nexus with the sales and profits associated with Viagra®. Trial Tr. 628:4-11, 633:17-23 (Hausman).

(c) Oral Treatment Of ED Is Not The Invention Of The '012 Patent

536. It is the earlier-issued '534 patent directed to the compound sildenafil and the chemical properties of that compound that are associated with the sales and profits of Pfizer's Viagra®, not the claims of the '012 method patent at issue in this proceeding. Trial Tr. 604:7-18 (Hausman).

537. Viagra's® efficacy in treating ED is a function of the chemical properties of sildenafil, which is claimed by the earlier-issued '534 compound patent. Trial Tr. 604:7-18 (Hausman); DX 2004 ('534 Patent).

538. Although oral administration is a limitation of claims 25 and 26 of the '012 patent, the oral treatment of ED is not the alleged "invention" covered by those claims. Trial Tr. 608:3–609:7 (Hausman).

539. Claim 26 is directed to the oral administration of sildenafil for the treatment of ED, and claim 25 is directed to the oral administration of sildenafil or eight other compounds for the treatment of ED. Trial Tr. 609:3-18 (Hausman).

540. Claims 25 and 26 of the '012 patent are not directed to, and do not cover, oral treatment of ED in general, (Trial Tr. 609:3-18 (Hausman)), and Pfizer's primary focus and business strategy for obtaining the '012 patent and the history of the '012 patent prove that oral administration is not the invention of the '012 patent. Trial Tr. 610:15-25, 614:8-13, 617:12-24, 618:8-11, 630:12-631:21 (Hausman).

541. Pfizer's primary focus for obtaining the '012 patent was to obtain a broad claim covering the oral administration of all PDE5 inhibitors for treating ED. Trial Tr. 610:15-25, 618:8-11 (Hausman). Pfizer had a $500 million incentive to keep other PDE5 inhibitors off the market because Pfizer's profits would be on the order of $500 million to $1 billion higher per

year if those products were kept off the market. Trial Tr. 610:15-25, 611:14-18, 611:25–612:6, 616:8-12 (Hausman).

542. Pfizer's product patent covering sildenafil, the '534 patent, does not cover competing PDE5 inhibitors for the oral treatment of ED, so the value of the '012 patent was to obtain a broad field of use claim that would allow Pfizer to keep all other competing PDE5 inhibitors off the market for the oral treatment of ED. Trial Tr. 611:1-6, 618:12-14 (Hausman).

543. Pfizer knew that Bayer and Eli Lilly were seeking FDA approval for competitor PDE5 compounds for the oral treatment of ED, but Pfizer did not have a means for keeping those two competing products off the market. Trial Tr. 618:15-619:20 (Hausman).

544. Pfizer had a business strategy to keep all PDE5 inhibitors off the market for the oral treatment of ED by attempting to obtain a broad field-of-use claim in the '012 patent based on its understanding that the scientific literature taught that PDE5 inhibitors would likely treat ED when administered orally. Trial Tr. 614:8-13, 617:12-618:11, 630:12-631:21 (Hausman).

545. The market actions that firms take are the most important indicators of the value of patent claims because those market actions reflect how business strategies play out in the real world. Trial Tr. 609:19–610:2 (Hausman). Business strategies are designed to maximize earnings for the company, which demonstrates where the market perceives value better than after-the-fact arguments in the context of litigation. Trial Tr. 610:3-9 (Hausman).

546. Viagra® was a major compound in Pfizer's commercial product portfolio, and the launch of one or more competitor compounds of the same class was clearly a major commercial interest to Pfizer. The whole effort with the application that issued as the '012 patent was directed to obtaining a broad claim that covered PDE5 inhibitors generally for the oral treatment of ED. Trial Tr. 619:7-20 (Hausman).

547. Despite the overwhelming economic incentive for Pfizer to obtain broad claims to the use of all PDE5 inhibitors for the oral treatment of ED, and despite Pfizer's business strategies to achieve that incentive, the U.S. Patent Office declared Pfizer's broad field-of-use claim invalid. Trial Tr. 614:14-19 (Hausman); DX 2303 at 55 (February 12, 2010 BPAI Decision).

548. Neither claim 25 nor 26 is the broad field-of-use claim that motivated Pfizer to obtain the '012 patent because those claims are not directed to and do not cover oral administration of the class of compounds of which sildenafil is a member – PDE5 inhibitors – for the oral treatment of ED. Trial Tr. 609:3-18 (Hausman).

549. Claim 24 of the '012 patent was directed to oral administration of any PDE5 inhibitor, any PDE5 inhibitor, to treat ED. DX 2001 ('012 Patent) Claim 24 was the "field of use" claim that, if valid, would have prevented competitors from marketing PDE5 inhibitors for oral treatment of ED. Trial Tr. 611:6-13, 612:7-17, 619:21-24 (Hausman).

550. Claim 24, however, was ruled invalid by the USPTO during reexamination of the '012 patent. Trial Tr. 611:18-24, 619:25-620:7 (Hausman); DX 2303 at 55 (February 10, 2010 BPAI Decision)).

551. On the day that the '012 patent issued in October 2002, Pfizer sued Eli Lilly and Bayer for alleged infringement of claim 24. Trial Tr. 612:18-24 (Hausman); DX 2300 (Bayer Complaint); DX 2301 (Lilly Complaint).

552. Eli Lilly (and ICOS) sought to market Cialis®, which contains the PDE5 inhibitor tadalafil, for the oral treatment of ED. Bayer (and Glaxo) sought to market Levitra®, which contains the PDE5 inhibitor vardenafil, for the oral treatment of ED. Trial Tr. 612:24–613:5 (Hausman).

553. The PDE5 inhibitors tadalafil (Cialis®) and vardenafil (Levitra®) are not among the PDE5 inhibitors identified in claims 1-23, 25 or 26 of the '012 patent and, therefore, claim 24 was the only claim at issue in the suits brought by Pfizer against Lilly and Bayer. Trial Tr. 613:6-11 (Hausman).

554. In November 2003, the Court stayed the lawsuits so that the USPTO could reexamine the validity of claim 24. Trial Tr. 613:12-14 (Hausman); DX 2304 (Memorandum Order to Stay Litigation).

555. During reexamination of the '012 patent, the USPTO Examiner rejected claim 24 on grounds that, among other things, the subject matter of claim 24, which the Examiner characterized as "treat[ing] male ED by oral administration of any selective PDEv inhibitor", is unpatentable as anticipated by the prior art. Trial Tr. 613:15-21 (Hausman); DX 2303 at 55 (February 10, 2010 BPAI Decision).

556. In February 2010, the Board of Patent Appeals and Interferences affirmed the Examiner's decision and agreed that prior art "references disclose oral administration of a selective PDEv inhibitor, i.e., icariin, in an amount effective to treat ED." Trial Tr. 613:21-22 (Hausman); DX 2303 at 30 (February 12, 2010 BPAI Decision)).

557. In March 2010, Pfizer and Lilly stipulated to a dismissal of their suit regarding Cialis®. Pfizer and Bayer settled their suit regarding Levitra® in 2004. Trial Tr. 613:13–614:1 (Hausman).

558. Pfizer has not been able to prevent Lilly and Bayer from marketing Cialis® and Levitra®, respectively, in the U.S. by asserting the '012 patent because the remaining claims of the '012 patent, including claims 25 and 26, cover the oral treatment of ED with specifically recited PDE5 inhibitors, not with any or all PDE5 inhibitors. Trial Tr. 614:2-7 (Hausman).

559. Cialis® and Levitra® have obtained substantial sales since their launch in 2003, and have taken approximately half of the sales in the PDE5 inhibitor category from Viagra®. Trial Tr. 614:22–615:4, 615:18–616:7, 617:2-11 (Hausman); DX 2306 (Sales for PDE5 Inhibitors); Maffezzoli Dep. Tr. at 55:24-56:21, 56:24-57:03, 57:25-58:11, 138:20-139:7. Usually, the first drug on the market, as was Viagra® for orally treating ED, maintains the majority share of the market. But, here, Cialis® and Levitra® have been quite successful in taking market share away from Viagra®. Trial Tr. 615:24–616:7 (Hausman); Maffezzoli Dep. Tr. at 65:22-24, 66:3-9.

560. Cialis® and Levitra®'s combined number of new prescriptions have surpassed the number of new prescriptions for Viagra® so that Viagra® now has less than half the market in terms of new prescriptions. Trial Tr. 616:13–617:11 (Hausman); DX 2307 (Prescriptions for PDE5 Inhibitors).

561. Given the amount of sales and prescriptions Viagra® has lost to Cialis® and Levitra®, Pfizer has a substantial economic incentive to stop their entry and expansion by asserting the '012 patent. Trial Tr. 614:8-18 (Hausman), 1044:24-1045:6 (Grabowski); Maffezzoli Dep. Tr. at 75:18-76:8, 181:15-24. Indeed, Pfizer's revenues would be on the order of $500 million to $1 billion higher on an annual basis if Cialis® and Levitra® were not available for sale given that Cialis® and Levitra® would not have eroded Viagra's® market share and Pfizer probably would have been able to charge higher prices for Viagra®. Trial Tr. 610:15-25, 611:14-18, 611:25–612:6, 615:5-17, 616:8-12 (Hausman), 1034:13-1035:1 (Grabowski).

562. Pfizer's inability to forestall the sales of Cialis® and Levitra®, despite its overwhelming economic incentive to do so, and the substantial sales obtained by those

competing products, demonstrates that claims 25 and 26 of the '012 patent are not responsible for Viagra's® sales and profits. Trial Tr. 608:3–609:7, 614:2–617:11 (Hausman).

563. Market outcomes arising from the profit-maximizing actions of firms are important indicators of the relative market position of competing products and a better indicator of whether there is a nexus between the sales and profits of a particular product or method and a particular patent than a priori statements about the scope of the claims. Trial Tr. 609:19–610:9 (Hausman).

564. Market outcomes for the competing PDE5 inhibitors used to treat ED and Pfizer's failure to forestall the substantial sales of Cialis® and Levitra®, which contain PDE5 inhibitors prescribed for the oral treatment of ED, demonstrate that there is no nexus between the sales and profits of Viagra® and claims 25 and 26 of the '012 patent, which cover the oral treatment of ED with the PDE5 inhibitor sildenafil. Trial Tr. 614:2–617:11, 620:8-17 (Hausman).

(d) Viagra's® Sales At The Time Of Launch Were Due, In Part, To Factors That Negate Its Commercial Success

565. The sales Viagra® obtained at the time of its U.S. launch were due, in part, to numerous factors that were unrelated to the inherent properties of Viagra®. Those other factors include the following:

- Pre-launch publicity that was cultivated by Pfizer;
- High levels of promotion at the time of launch; and
- An aggressive distribution plan that reduced the typical time needed to obtain nationwide distribution by 75%.

i. Pre-Launch Publicity Cultivated By Pfizer

566. Viagra® was the subject of substantial publicity prior to and at the time of its launch. That publicity was cultivated by Pfizer.

567. A speech given by David Brinkley, Pfizer's team leader for Viagra®, at the Viagra® Managers Launch Meeting in early April 1998 describes the amount of publicity at the time, and Pfizer's role in generating that publicity. DX 2294 at PFZ02993411-3425 (Viagra® Manager Launch Meeting).

568. According to Mr. Brinkley, Viagra® was approved at 10:46 AM on March 27, 1998, and "Pfizer held its first ever drug approval press conference" at 2:30 PM that same afternoon. DX 2294 at PFZ02993420 (Viagra® Manager's Launch Meeting).

569. As explained by Mr. Brinkley:

> Our objective was to lay the groundwork for the marketing of Viagra by generating favorable coverage in print and broadcast media. The coverage exceeded our most optimistic expectations. From late Friday morning on March 27th, through that Sunday night . . . Viagra was front-page news across America. We had set the tone the previous week with an extraordinarily positive story on the ABC newsmagazine "20/20." … But while the 20/20 piece reached millions in prime time, it really just set the stage for what happened next. The story of Viagra's approval received intense, coast-to-coast coverage. It was front page news in many of the most influential papers in the country. The Associated Press ran a story that was three times longer than usual for a new drug, and it appeared in over 60 newspapers with a combined circulation of greater than 20 million. Together with a front-page story in USA Today, it is clear that our message was heard in the big cities . . . and small towns across America. On television, we had a prominent story on CNN that featured excerpts from our press conference . . . coverage on the major broadcast networks . . . and stories on stations around the country. Many stations used interviews with local medical experts who had already received speakers bureau training from Pfizer. There was coverage on The Today Show and Tom Brokaw's Nightly News that alone reached 18 million viewers. And our video news release, added another 200 stations and 60 million viewers. Between the television and print coverage, we reached 46 of the top 50 markets . . . a level of exposure unheard-of for a new pharmaceutical.

DX 2294 at PFZ02993421-3423 (Viagra® Manager's Launch Meeting).

570. The "unheard-of" exposure described by Mr. Brinkley resulted from a deliberate strategy on the part of Pfizer during the pre-launch period for Viagra®. DX 2285 at PFZ03325762 (September 1997 Global Marketing Plan).

571. In September 1997, Pfizer distributed a Global Marketing Plan for Viagra®, which according to the Executive Summary, was intended to serve "as the basis for the global introduction of Viagra® (sildenafil)." DX 2285 at PFZ03325735 (September 1997 Global Marketing Plan).

572. The number one objective of Pfizer's Global Marketing Plan was to "Prepare the product and the market for a successful and rapid launch worldwide," and the strategies to meet that objective included "Establish[ing] the promotional platform," "Creat[ing] disease awareness," "Develop[ing] opinion leaders to support VIAGRA worldwide," and "Manag[ing] the media and develop[ing] relationships and programs with patient advocacy groups to ensure that the correct messages are being disseminated to the public." DX 2285 at PFZ03325762 (September 1997 Global Marketing Plan).

573. One of the "Opportunities" noted by the Global Marketing Plan is "High media attention at launch to allow rapid take-off." DX 2285 at PFZ03325765 (September 1997 Global Marketing Plan). The Global Marketing Plan further states that "[a]s an ideal pre-launch activity, this [disease awareness] program will be started <u>now</u> and rolled out through the launch and post-launch phases of the product." DX 2285 at PFZ03325770 (September 1997 Global Marketing Plan).

574. As an example of a disease awareness activity, in March 1998 Pfizer distributed three general article templates on ED awareness to the press. DX 2287 at PFZ03003050 (March 1998 Pfizer ED Awareness Templates).

575. A September 1997 Pfizer Document entitled "Viagra: Communications Management for a Breakthrough Therapy" identifies several strategies to implement during the pre-approval and pre-launch periods. DX 2296 at PFZ00898192 (September 1997 Viagra® Communications). Among the "Stage 1: Pre-approval actions" are "Develop[ing] communications materials," "Identify[ing] and media-train[ing] broad base of third-party supporters," "Background briefings with influential reporters to set tone of coverage," and "Target[ing] most influential media." DX 2296 at PFZ00898209-8210 (September 1997 Viagra® Communications).

576. Among the "Stage 2: Actions between approval and launch" are "Targeted media briefing in New York, other key cities," "Educational tour or 'road show'," "Broad-based mailing to media," and "Identify[ing] 'success stories' from trials to humanize issues for media." DX 2296 at PFZ00898211-8212 (September 1997 Viagra® Communications).

577. The November 1997 Operating and Launch Plan for Viagra® called for a "Fast Start to Introduce Viagra," including "Public Relations to Launch Viagra Very Visibly," "Large-scale, State-of-the-Art Press Conference at Approval," "Press Briefings for Most Influential Media," "Maximiz[ing] Availability of National/Regional Opinion Leaders to Key Media," and "Develop[ing] Viagra Story Angles for Diverse Media." DX 2290 at PFZ03021311 (November 1997 Operating and Launch Plan).

578. Minutes from an October 1997 Viagra® GDT meeting discuss "PR Plans" that include "Us[ing] the media to educate public about ED (pre-launch) and Viagra (post-launch)," "Fully leverag[ing] early 'window of opportunity'," "Cultivat[ing] national and regional opinion leaders familiar to media," and "Within 48 hours of FDA approval, conduct[ing] large-scale press conference." DX 2289 at PFZ00890234 (October 1997 Viagra® GDT Meeting). Minutes

from a January 1998 Viagra® GDT meeting state that the objectives for the "PR Plan" in 1998 included "rapid recognition" and "generat[ing] coverage."

579. As a result, in part, of the enormous wave of publicity that Pfizer cultivated, Viagra® prescriptions immediately after launch were high. DX 2291 at PFZ03021075 (1999 U.S. Operating Plan); DX 2297 at PFZ03021812, 1832 (Viagra® Maximizing Media Attention).

580. Viagra® prescription volume fell soon after launch. DX 2292 at PFZ04275602, 5610 (Viagra® 2000 Operating Plan).

581. Viagra's® 1999 Operating Plan notes that new prescriptions for Viagra® dropped from a peak of 275,000 in May 1998 to 85,000 in August 1998. DX 2291 at PFZ03021075 (1999 U.S. Operating Plan). As one explanation for the decline, the Plan states "this early spike in prescriptions is made up partly by product trial, some of which may be non-sustainable. DX 2291 at PFZ03021075 (1999 U.S. Operating Plan). The tremendous publicity around Viagra probably led men to try Viagra® regardless of their erectile function." DX 2291 at PFZ03021075 (1999 U.S. Operating Plan). The Plan goes on to state "the amount of media attention given to Viagra® is estimated at $50 million (if it were to have been purchased)," and "this attention is responsible for the high levels of awareness of the product." DX 2291 at PFZ03021075 (1999 U.S. Operating Plan).

582. A document entitled "Maximizing Media Attention" states "[t]he launch of VIAGRA® in the US has been the most phenomenal prescription-drug launch in history. Even though the US launch occurred several months ago, journalists continue to create new story angles and report on VIAGRA® almost daily. Because VIAGRA has captured the attention of the world, country organizations have a unique opportunity to maximize media interest for their own launches." DX 2297 at PFZ03021812 (Viagra®: Maximizing Media Attention). The

document goes on to state "[i]n the weeks preceding US approval, journalists contacted Pfizer daily for comment on VIAGRA and wrote stories in anticipation of the FDA decision … Within 24 hours of receiving official FDA notification, Pfizer held a press conference in New York for US print and broadcast media … The result of the press conference was extensive media coverage of VIAGRA around the world. In the first week after FDA approval, more than 130 million media impressions were generated in the U.S. alone." DX 2297 at PFZ03021832 (Viagra®: Maximizing Media Attention).

583. A September 1998 presentation at the Viagra® European Communicators' Conference notes that "Effective media management [is] essential to commercial success." DX 2284 at PFZ00225679 (September 1998 European Communicators' Conference).

ii. High Levels Of Promotion By Pfizer At The Time Of Launch

584. Another factor contributing to the high level of Viagra® sales shortly after the time of launch was the high level of detailing (promotional visits by sales representatives to doctors) and other types of promotion for Viagra® at the time of launch. The level of detailing and other types of promotion for Viagra® was high at the time of launch, and Pfizer recognized that this detailing drove Viagra® prescriptions.

585. High levels of promotion by Viagra®'s field force were part of Pfizer's launch plan for Viagra®. DX 2285 (September 1997 Global Marketing Plan)

586. According to the Global Marketing Plan for Viagra®, "the best allocation [for the field force] would be the configuration that allows rapid take off by laying a strong foundation at the time of launch." DX 2285 at PFZ03325788 (September 1997 Global Marketing Plan).

587. Pfizer recognized the connection between detailing and the early success of Viagra® in its 2000 Operating Plan. According to the Plan, both total prescriptions and new

prescriptions for Viagra® peaked in April-May 1998 and then fell off to lower levels. DX 2292 at PFZ04275602, PFZ04275602-5610 (Viagra® 2000 Operating Plan). The Plan recognized that the amount of detailing for Viagra® followed exactly the same pattern, peaking immediately after the time of launch. DX 2292 at PFZ04275608 (Viagra® 2000 Operating Plan). The Plan includes a chart of both new prescriptions and details that shows the close relationship between detailing and new prescriptions of Viagra®. DX 2292 at PFZ04275611 (Viagra® 2000 Operating Plan). Other types of promotion for Viagra® (sampling and physician meetings and events) also peaked in April-May 1998, corresponding to the early peak in Viagra® sales. DX 2282 (Viagra® Samples & Units); DX 2283 (Viagra® PMBA Expenditures & Units).

588. The Plan goes on to state that "Representative Activity Influences Prescribing Behavior," noting that the number of prescriptions per specialist is higher for specialists who were detailed. DX 2292 at PFZ04275612 (Viagra® 2000 Operating Plan). The Plan also states that one of the "Major Issues/Opportunities" for Viagra® is that "Details drive NRx [new prescriptions]." DX 2292 at PFZ04275623 (Viagra® 2000 Operating Plan).

589. A September 1998 presentation on the "Early Performance of Viagra" also concludes that detailing drives Viagra® prescriptions. The presentation states that "Detailing [Is] Associated With Higher Levels of Viagra Prescribing," and concludes that "Detailing Is Effective and Proven." DX 2284 at PFZ00225660 at PFZ00225673 (September 1998 European Communicators' Conference).

590. A February 1999 presentation on Viagra® sales notes that Viagra® had received "Unprecedented Education and Detailing Support," and that Viagra® was the "[m]ost detailed product in [the] U.S." DX 2295 at PFZ04396986 (2002 Operating Plan).

591. A May 2000 presentation states that Viagra® prescribers "Are Responsive to Detailing," noting that that the highest cardiovascular prescribers were the ones who received the most Viagra® details in 1999. DX 2288 at PFZ03233544 (May 2000 POA). The presentation goes on to state that "Detailing Is Critical." DX 2288 at PFZ03233550 (May 2000 Operating POA). The 2001 Operating Plan for Viagra® also notes that "More Frequent Detailing = More Prescriptions." DX 2293 at PFZ03243839 (December 2000 Global Operating Plan).

592. The 2002 Operating Plan for Viagra® states that "Sales Presentations Drive Prescribing," and that "MDs Called on 3+/Month Write Significantly More Viagra." DX 2295 at PFZ04396986 (2002 Operating Plan). In addition to the level of Viagra® prescription being higher for doctors who receive more details, the growth in prescriptions is also higher, as the Plan notes that "Growth in Rxing Among MDs Called on 3+/Month Significantly Greater." DX 2295 at PFZ04396986 (2002 Operating Plan).

iii. Pfizer's Aggressive Distribution Plan For Viagra®

593. One factor contributing to the level of initial sales of Viagra® was that Pfizer had to fill the distribution pipeline at the time of launch by distributing Viagra® to wholesalers and retailers.

594. Pfizer's 10-Q for the second quarter of 1998 states "Viagra was our second-largest selling product worldwide and our largest selling U.S. product with U.S. sales of $409 million. DX 2309 (Pfizer Form 10Q filed 8/11/1998). The initial rate of sales reflects prescriptions and substantial trade stocking, which we expect will adjust to be consistent with underlying demand over the remainder of the year." DX 2309 (Pfizer Form 10Q filed 8/11/1998).

595. Pfizer's 10-Q for the third quarter of 1998 notes that Viagra® sales fell from $409 million in the second quarter to $141 million in the third quarter "due to wholesaler stocking in

the U.S. in the second quarter and an expected reduction in prescription levels in the third quarter." DX 2310 (Pfizer Form 10Q filed 11/12/1998).

596. Pfizer took a particularly aggressive approach to filing the distribution pipeline with Viagra®, which contributed to the high level of initial sales.

597. In a speech prepared for the April 1998 Viagra® launch meeting, the Pfizer employees from the group that distributes product to wholesalers and retail pharmacies described the distribution process and stated that "the time required to achieve national distribution at the pharmacy level is normally about eight weeks after FDA approval." DX 2294 at PFZ02993847-49 (April 1998 Viagra® Managers Launch Meeting).

598. For Viagra®, Pfizer developed a new program called the "Rapid Distribution Program" that was intended to reduce the time required to obtain national distribution by 75%, from 8 weeks to 2 weeks. DX 2294 at PFZ02993851-52 (April 1998 Viagra® Managers Launch Meeting). Thus, the April 1998 sales of $248 million do not reflect the inherent level of demand for Viagra®, but rather an aggressive distribution program in which two months' worth of sales were compressed into two weeks.

2. Viagra® Has Not Satisfied Any Long-Felt, Unmet Need

599. There was no long-felt need for a method of treating ED with sildenafil in particular. There is no nexus between any long-felt need, if any, satisfied by Viagra® and claims 25 and 26 of the '012 patent. Trial Tr. 608:3-20 (Hausman).

600. By June 1993 a POSA would have understood how to use a selective PDE5 inhibitor to treat ED, and would have known that sildenafil is a selective PDE5 inhibitor. *Supra* Section IX.A-E (obviousness); Trial Tr. 617:12-24, 630:12-631:21 (Hausman).

601. The reason that there was no effective oral treatment for ED with sildenafil prior to Viagra® is that Pfizer controlled the compound sildenafil. Trial Tr. 604:7-606:31 (Hausman).

That has nothing to do with the invention claimed in the '012 patent, which is a method of using sildenafil, a method that would have been obvious to a POSA. *Supra* Section IX.A-E.

602. Claims 25 and 26 cover a method of using prior art compounds to treat ED. Those prior art compounds are covered by other patents. Therefore, to the extent that Pfizer asserts that a long-felt need existed for the product – *i.e.*, Viagra® – that does not shed light on the non-obviousness of the methods recited in claims 25 and 26 of the '012 patent.

603. Viagra® did not meet any unmet need. When Cialis® and Levitra® became available they gained substantial sales and prescriptions, despite the availability of Viagra®. Trial Tr. 614:22-615:4, 615:18-617:11 (Hausman); DX 2306 (Wholesale Dollar Sales for PDE5 Inhibitors); DX 2307 (New Prescription for PDE5 Inhibitors). If Viagra® had met any need, there would have been no need for Cialis® and Levitra®.

3. The Chemical And Biological Properties Of Viagra® Are Not Unexpected

604. A POSA would reasonably have expected that the subject matter in claims 25 and 26 of the '012 patent would be effective for treating ED by oral administration. *Supra* Section IX.A-E (Obviousness).

605. There is no evidence of a nexus between the claimed "invention" and any alleged unexpected results. Sildenafil and its chemical properties are claimed in the'534 patent, which was in the prior art. Trial Tr. 604:7-18 (Hausman). Any nexus to sildenafil's properties can be attributed to the '534 patent, not the '012 patent. Trial Tr. 627:15-21 (Hausman).

4. Any Alleged Copying Does Not Suggest That The Asserted Method Claims Are Not Obvious

606. Several companies were developing PDE5 inhibitors before the introduction of Viagra®, and even before Pfizer filed the application that issued as the '012 patent. *See, e.g.*, Trial Tr. 413:18-415:25 (Corbin). There is no nexus between any alleged copying of Viagra®

and claims 25 and 26 of the '012 patent because competitors of Pfizer developed PDE5 inhibitors whose use is not covered by those claims. Trial Tr. 600:5-608:2 (Hausman).

607. Beginning in the 1991–1992 timeframe, Dr. Corbin was directly involved with Glaxo (later transferred to ICOS) in developing Cialis®. Trial Tr. 413:18-415:25 (Corbin). Like Pfizer, some of these companies started their projects by developing PDE5 inhibitor drugs to target cardiovascular disease, but then switched to target ED. Trial Tr. 413:18-415:25 (Corbin).

608. Glaxo's WO 97/03675 ("WO '675'") has some of the same language as Pfizer's WO 94/28902 ("WO '902'"). That is not evidence of copying. The disclosed compounds also are different. Compare PTX0279 (WO 97/03675) to DX 2013 (WO 94/28902).

5. Any Alleged Praise Or Recognition For Viagra® Does Not Suggest That The Asserted Method Claims Are Not Obvious

609. Any praise that has been directed to the product, Viagra®, reflects praise generally for the oral treatment of ED, which is not covered by claims 25 and 26 of the '012 patent. Trial Tr. 792:9-17 (Ellis).

6. The Evidence Does Not Support Any Skepticism About Or Teaching Away From The Obviousness Of The Subject Matter Claimed In Claims 25 And 26 Of The '012 Patent

610. Systemic effects of the compound relate to potential adverse effects of the compound, and not the compound's therapeutic effect.

611. Claims 25 and 26 of the '012 patent do not contain any element that relates to side effects. Trial Tr. 277:4-6 (Carson), 358:24-359:22 (Corbin). Indeed, sildenafil has some side effects. Trial Tr. 228:18-229:1 (Carson). A POSA would have had a reasonable expectation of effectively treating ED, *i.e.*, facilitating erections, by orally administering a selective PDE5 inhibitor, such as sildenafil. DX 2303 at 51-52 (02/12/10 BPAI Decision).

7. The Alleged Failure Of Other Companies To Develop PDE5 Inhibitors For Treating ED Does Not Establish That Claims 25 And 26 Are Not Obvious

612. In June 1993, a POSA would have reasonably expected that a selective PDE5 inhibitor, such as sildenafil, would be effective orally to treat ED. *Supra* Section IX.D.5 (obviousness). A POSA, however, could not have used sildenafil to treat ED because the compound was under Pfizer's exclusive control. Trial Tr. 229:23-230:7, 279:20-280:2 (Carson), 600:21-25 (Hausman). Moreover, there is no nexus between the alleged failure of others to develop PDE5 inhibitors for treating ED and claims 25 and 26 of the '012 patent because those claims do not cover treating ED with all PDE5 inhibitors. Trial Tr. 609:3-18 (Hausman).

613. At the same time that Pfizer was developing sildenafil for the treatment of ED, other companies were developing PDE5 inhibitors that researchers recognized could be useful for treating ED. Trial Tr. 270:6-271:6, 289:12-290:17 (Corbin).

614. Although some of those companies were developing PDE5 inhibitors for cardiovascular disease, as was Pfizer at that time, those companies understood that their own PDE5 inhibitor compounds could treat ED. Trial Tr. 413:18-415:25 (Corbin).

615. For example, Glaxo, in partnership with ICOS Corporation, began developing PDE5 inhibitors in 1988 (that project was later inherited by Eli Lilly, which worked with ICOS Corporation). Trial Tr. 413:18-415:25 (Corbin).

616. Researchers collaborating with Glaxo understood that PDE5 inhibitors had therapeutic potential for treating ED as early as November 1991. Trial Tr. 179:16-189:19, 182:15-183:8, 289:12-290:17 (Carson), 413:18-415:25 (Corbin); DX 2459 at 1 (Corbin Letter to Schrago); DX 2455 at 2-3 (Corbin Letter to Ross); DX 2267 at 1 (Glaxo/Corbin Research Project).

617. Glaxo filed a patent application covering the use of a PDE5 inhibitor to treat ED in mid-1995, suggesting that Glaxo/ICOS (and later Lilly) moved relatively quickly to patent the use of PDE5 inhibitors for treating ED. Trial Tr. 177:2-180:19 (Corbin).

618. Pfizer synthesized numerous potent and selective PDE5 inhibitors by 1990, ahead of the rest of the industry, for the treatment of hypertension and angina. Terrett Dep. Tr. at 132:6-136:9. Pfizer synthesized sildenafil in 1989 as part of that project. DX 2302 at 21 (Ellis Canadian Declaration).

619. Those PDE5 inhibitors, including sildenafil, were disclosed in EP '756 and other prior art Pfizer patent applications. *See* DX 2004 ('534 patent); DX 2006 (EP '004); DX 2068 (WO '104); DX 2074 (EP '756). Pfizer was the first to have the compounds and therefore was also the first to actually use the compounds to treat ED.

620. Pfizer started Phase I clinical trials for sildenafil in July 1991 to support Phase II and III testing for angina, allegedly before it observed that sildenafil could potentially treat ED. DX 2302 at 26 (Ellis Canadian Declaration).

621. The "goal of Pfizer's Phase I studies was primarily to assess the safety, toleration, and pharmacokinetics of sildenafil," meaning that the studies were not disease-specific. DX 2302 at 34 (Ellis Canadian Declaration); Terrett Dep. Tr. at 44:8-46:11.

622. Pfizer completed several Phase I studies of sildenafil by February 1992. DX 2302 at 26, 27, 34 (Ellis Canadian Declaration).

623. By April 1992, Pfizer received a report regarding a Phase I study that indicated that volunteer subjects reported "prolonged and spontaneous erections." DX 2302 at 35-37 (Ellis Canadian Declaration).

624. Pfizer began a Phase II study of sildenafil for treating ED in July 1993. DX 2302 at 49 (Ellis Canadian Declaration).

625. Pfizer had been working with sildenafil for four years. That is why Pfizer was the first to market an orally administrable PDE5 inhibitor for the treatment of ED. Trial Tr. 603:4-22 (Hausman).

X. CLAIMS 25 AND 26 OF THE '012 PATENT ARE NOT PATENTABLY DISTINCT FROM CLAIM 1 OF THE '270 PATENT

626. Claims 25 and 26 of the '012 patent are invalid for obviousness-type double patenting over claim 1 of U.S. Patent No. 6,100,270 ("the '270 patent"), in view of the general knowledge of a POSA, as evidenced by International Application Publication No. 93/06104 ("WO '104"), EP '756 and EP '004. Corbin Direct at 382:23–383:9; 398:24–399:19.

627. The face of the '270 patent and the face of the '012 patent state that those patents were assigned to Pfizer Inc. DX-2066 at cover, at (73); DX-2001 at cover, at (73).

A. The '012 Patent

628. The term of the '012 patent expires on October 22, 2019. SUF ¶ 9.

629. Claim 25 of the '012 patent is reproduced below:

> **25**. A method of treating erectile dysfunction in a male human, comprising orally administering to a male human in need of such treatment an effective amount of a compound selected from:
> 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
> 5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
> 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one;

5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinyl-sulphonyl] phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one; and
5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
or a pharmaceutically acceptable salt thereof;
or a pharmaceutical composition containing either entity.

DX-2001 at 10:1–33 (‘012 patent).

630. Claim 26 of the ‘012 patent depends from claim 25 and is reproduced below:

26. A method as defined in claim **25**, wherein said compound is 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

DX-2001 at 10:34–39.

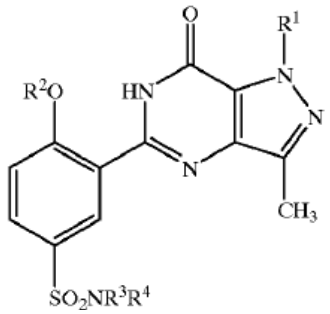
631. The compounds recited for use in the methods of claims 25 and 26 of the ‘012 patent were disclosed in the prior art references EP ‘756 and EP ‘004. DX-2074 at 3:19–49, 4:15–29 (EP ‘756); DX-2006 at 2:19–49, 3:25–34 (EP ‘004); Trial Tr. 326:13–20 (Corbin).

B. **The ‘270 Patent (DX 2066)**

632. The ‘270 patent, titled “Bicyclic Heterocyclic Compounds for the Treatment of Impotence,” issued on August 8, 2000. DX-2066 at cover, at (54) (‘270 patent) Trial Tr. 383:10–384:9 (Corbin).

633. The term of the ‘270 patent expires on October 16, 2015.

634. Claim 1 of the '270 patent claims a method of treating ED in a male human by administering an effective amount of a compound having a formula set forth in the claim. DX-2066 at 8:8–31 ('270 patent). Claim 1 of the '270 patent is reproduced below:

> **1**. A method of treating male erectile dysfunction comprising administering to a male human in need of such treatment an effective amount of a compound of formula (I):
>
> (I)
>
> 
>
>
> wherein R^1 is methyl or ethyl;
> R^2 is ethyl or n-propyl;
> and R^3 and R^4 are each independently H, or C_1–C_6 alkyl optionally substituted with
> C_5–C_7 cycloalkyl or with morpholino; or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

DX-2066 at 8:8–31 ('270 patent).

635. The compounds recited for use in the method of claim 1 of the '270 patent were disclosed in the prior art reference WO '104. DX-2068 at 2 ('270 patent); Trial Tr. 385:4–12, 387:14–388:5 (Corbin); Trial Tr. 955:16–25 (Terrett).

C. **A One-Way Test For Obviousness-Type Double Patenting Is Warranted**

636. During reexamination, the USPTO considered whether claim 24 of the '012 patent was invalid for obviousness type-double patenting over claim 1 of the '270 patent and found that Pfizer was "not entitled to the two-way test of obviousness" because the applicants for the '012 patent "could have filed patents in a single application" and the record failed establish "that there was an administrative delay due solely to the PTO." PTX0005 at PFZFH0051782–833 (Feb. 10, 2005 Office Action), at PFZFH0051828, at ¶ 86.

1. The Claims At Issue Are In The Patent That Issued From The Earlier Filed Application

637. The claims at issue are in the ‘012 patent. The ‘012 patent issued from an application that was filed (May 13, 1994) (DX 2001 at cover, at (22) (‘012 patent)), which is earlier than the filing date of the application for the ‘270 patent (October 16, 1995). DX 2066 at cover, at (22) (‘270 patent), DX 2013 at cover, at (22) (WO ‘902).

2. The Applicants For The ‘012 Patent Could Have Filed Claims 25 And 26 Of The ‘012 Patent And Claim 1 Of The ‘270 Patent In A Single Application

638. EP ‘756, EP ‘004 and WO ‘104 were published before the application for the ‘012 patent was filed, and disclose compounds that are selective inhibitors of PDE5. DX 2074 at 3:1–7, 7:6–7 (EP ‘756); DX 2240 at 4 (Ellis Declaration); DX 2006 at 2:1–7, 8:53–54, 26:1–35 (EP ‘004); DX-2068 at 1, 2, 8, 17–19 (WO ‘104).

639. When the ‘012 patent issued, it included claim 24, which was directed to the use of any selective PDE5 inhibitor for the treatment of ED in humans. DX-2001 at 9:36–41 (‘012 patent).

640. The Patent Office stated that the applicants for the ‘012 patent could have included in the application for the ‘012 patent the use of the compounds disclosed in EP ‘756, EP ‘004 and WO ‘104 for the treatment of ED, but chose to include only the use of the compounds disclosed in EP ‘756 and EP ‘004. PTX0005 at PFZFH0051782–833 at PFZFH0051825–26, at ¶¶ 82–83 (Feb. 10, 2005 Office Action).

641. The Patent Office stated that Claims 25 and 26 of the ‘012 patent and claim 1 of the ‘270 patent could have been filed in a single application. PTX0005 at PFZFH0051782–833 at PFZFH0051826 at ¶¶ 82–83 (Feb. 10, 2005 Office Action).

642. In the early 1990s, Pfizer sought to protect its intellectual property in sildenafil by filing patent applications to prevent competitors from making equivalents to sildenafil by making small changes to sildenafil's structure. Campbell Dep. Tr. at 110:18–112:08, 131:08–131:11, 131:12–131:14, 134:18–135:08.

643. Pfizer filed the application for the '270 patent because Dr. Campbell felt that the method of use claims of the Terrett and Ellis application (*i.e.*, the application for the '012 patent) could have been broader to cover the use of other selective cGMP PDE inhibitors (*e.g.*, the compounds of WO '104) that Pfizer had synthesized that were not specifically covered by the claims of the Terrett and Ellis application. Campbell Dep. Tr. at 131:08–131:11, 131:12–131:14, 134:18–135:08. Dr. Campbell therefore suggested that Pfizer file a patent application directed to the use of those other compounds for the treatment of ED, even though those compounds had not been clinically tested for ED. Campbell Dep. Tr. at 131:08–131:11, 131:12–131:14, 134:18–135:08.

644. During reexamination, the USPTO recognized that "in particular, the compounds used in the method of treating erectile dysfunction of patents Campbell '270 and '511 were known to be selective cGMP PDE_v inhibitors before the filing of the Ellis '012 patent," "at the time of filing claim 24 in the Ellis '012 patent, the Patent Owner could have included in the specification other selective cGMP PDE_v inhibitors known at that time but chose not to do so," and that "[t]herefore, the Patent Owner is not entitled to the analysis of claim 24 under the two-way test of obviousness." PTX0005 at PFZFH0051782–833 at PFZFH0051825–26 at ¶¶ 82–83 (Feb. 10, 2005 Office Action).

3. To The Extent There Was Any Administrative Delay In The Prosecution Of The Application For The '012 Patent That May Have Caused The '012 Patent To Issue After The '270 Patent Issued, The USPTO Was Not Solely Responsibility For That Delay

645. To the extent there was any administrative delay in the prosecution of the application for the '012 patent that caused the '012 patent to issue after the '270 patent issued, the USPTO was not solely responsible for that delay. PTX0005 at PFZFH0051782–833 at PFZFH0051827–88 at ¶ 85 (Feb. 10, 2005 Office Action).

646. The applicants for the '012 patent were active participants in the appeals process during prosecution, having filed papers that prolonged the appeals process, including a February 10, 1998 Notice of Appeal (PTX0004 at PFZFH0010762–63) together with a petition for a 3-month extension of time (PTX0004 at PFZFH0010761), an April 10, 1998 affidavit (PTX0004 at PFZFH0009724–26), an August 5, 1998 Brief for Appellants (PTX0004 at PFZFH0010941-80) together with a petition for a 4-month extension of time (PTX0004 at PFZFH0010940), and a January 5, 1999 Reply Brief (PTX0004 at PFZFH0002791-811). PTX0005 at PFZFH0051782–833 at PFZFH0051827–88 at ¶ 85 (Feb. 10, 2005 Office Action).

647. During reexamination, the USPTO recognized that the applicants for the '012 patent "did not simply file the Appeal Brief and wait 3 years and 6 months for a decision," that they were "active participant[s] in this delay by filing declarations and other papers such as information disclosure statements," and that therefore, "the delay was not solely attributable to the PTO." PTX0005 at PFZFH0051782–833 at PFZFH0051827–88 at ¶ 85 (Feb. 10, 2005 Office Action).

D. The Methods Of Claims 25 And 26 Of The '012 Patent Are Not Patentably Distinct From The Method Of Claim 1 Of The '270 Patent

1. The Differences Between The Claims

648. With the exception of the following differences, claims 25 and 26 of the '012 patent and claim 1 of the '270 patent cover identical subject matter:

(a) claims 25 and 26 of the '012 patent require oral administration, whereas claim 1 of the '270 patent does not recite a particular route of administration; and

(b) the compounds recited for use in the methods of claims 25 and 26 of the '012 patent differ in structure from the compounds recited for use in the method of claim 1 of the '270 patent.

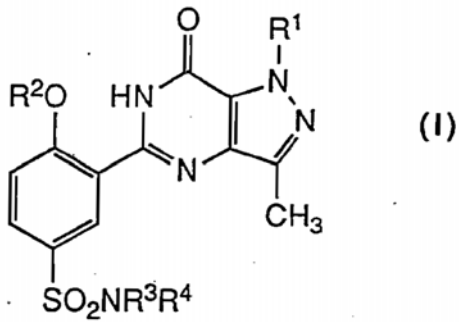
Trial Tr. 391:25–392:9, 398:23–399:25 (Corbin).

2. The General Knowledge Of A POSA

(a) WO '104 (DX 2068)

649. WO '104 was published April 1, 1993. DX-2068 at cover, at (43) (WO '104); Trial Tr. 337:16–25, 385:20–21 (Corbin).

650. WO '104 discloses compounds of formula (I), set forth below:



(I)

R^1, R^2, R^3 and R^4 represent potential substituents, as set forth in WO '104. DX-2068 at 2 (WO '104); Trial Tr. 387:14–25 (Corbin).

651. Formula (I) of WO '104 encompasses billions of compounds that share a common core ring structure but whose substituents differ at R^1, R^2, R^3 and/or R^4. DX-2068 at 2 (WO '104); Trial Tr. 400:5-15 (Corbin).

652. WO ‘104 contains a table titled: “In Vitro Inhibitory Activity And Selectivity Against The Ca/CAM-Independent cGMP PDE And The cGMP-Inhibited cAMP PDE·Enzvmes.” DX-2068 at 17–19 (WO ‘104). That table discloses *in vitro* PDE inhibitory data for 4 of the compounds disclosed in WO ‘104. DX-2068 at 18–19, at Examples 1–4 (WO ‘104).

653. A POSA would have understood “calcium/calmodulin (Ca/CAM)-independent cGMP PDE” to mean PDE5, and “cGMP-inhibited cAMP PDE” to mean PDE3. Trial Tr. 336:1–15, 332:9–14, 331:25–332:8 (Corbin). A POSA therefore would have understood the table in WO ‘104 to disclose *in vitro* inhibitory activity against PDE5 and PDE3 for 4 of the compounds of formula (I) of WO ‘104, and each compound’s selectivity for PDE5 over PDE3. Trial Tr. 336:1–15, 332:9–14, 331:25–332:8 (Corbin).

654. The table in WO ‘104 discloses the following inhibitory data for those 4 compounds:

Compound Reference	IC_{50} v. cGMP PDE	IC_{50} v. cAMP PDE	Selectivity Ratio
Example 1	0.13 µM (130 nM)	~10 µM (~10,000 nM)	~769
Example 2	0.0048 µM (4.8 nM)	11 µM (11,000 nM)	2292
Example 3	0.0048 µM (4.8 nM)	1.2 µM (1,200 nM)	250
Example 4	0.0047 µM (4.7 nM)	18 µM (18,000 nM)	3,830

DX-2068 at 18–19, at Examples 1–4 (WO ‘104).

655. A POSA would have interpreted the IC_{50} value in the column labeled “IC_{50} v. cGMP PDE” to mean the example compound’s IC_{50} value for inhibition of PDE5. Trial Tr. 341:13–343:4 (Corbin). A POSA would have interpreted the IC_{50} value in the column labeled

"IC_{50} v. cAMP PDE" to mean the example compound's IC_{50} value for inhibition of PDE3. Trial Tr. 341:13–343:4 (Corbin).

656. A POSA would have understood the IC_{50} data in the table of WO '104 to mean that the 4 tested compounds, especially Examples 2–4, are highly potent inhibitors PDE5, weak inhibitors of PDE3 and, consequently, highly selective for inhibition of PDE5 over inhibition of PDE3. Trial Tr. 341:13–343:4 (Corbin).

657. A POSA would have understood WO '104 to disclose that all of the compounds of formula (I) are potent and selective inhibitors of PDE5. Trial Tr. 338:1-339:2, 341:13–343:4 (Corbin).

658. WO '104 teaches that the compounds of formula (I) may be administered orally, in a range of 4-800 mg/day, in single or multiple doses, once or several times per day:

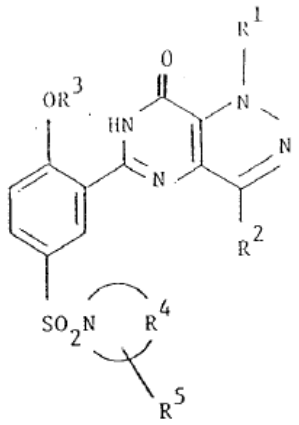
> For administration to man in the curative or prophylactic treatment of angina, hypertension or congestive heart failure, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day.

DX-2068 at 8–9 (WO '104); Trial Tr. 388:6–23 (Corbin). That dosage range encompasses the preferred dosing regimen of 5-75 mg of compound three times per day disclosed in the '012 patent. *See* DX 2001 at 5:65-66 ('012 patent).

659. By May 13, 1994, a POSA would have known that the compounds disclosed in WO '104 are potent and selective inhibitors of cGMP PDE, including PDE5, that are useful in the treatment of at least a dozen specified disorders and that those compounds could be administered orally in a range of 4-800 mg per day. DX-2068 at 1 (WO '104); Trial Tr. 338:1–339:2 (Corbin).

(b) EP '756 (DX 2074)

660. EP '756, which published on January 2, 1992. DX-2074 at cover, at (43) (EP '756). EP '756 discloses compounds of formula (I), set forth below:



(I)

R^1, R^2, R^3, R^4 and R^5 represent potential substituents, as set forth in EP '756. DX-2074 at 3:19–49 (EP '756).

661. Formula (I) of EP '756 encompasses at least millions of compounds that share a common core ring structure but whose substituents differ at R^1, R^2, R^3, R^4 and/or R^5. DX-2074 at 3:19–49 (EP '756); Trial Tr. 400:16–19 (Corbin).

662. EP '756 discloses that the compounds of formula (I) are potent and selective inhibitors of both cGMP PDEs, *i.e.*, PDE1 and PDE5, and that based on that inhibitory activity profile the compounds of formula (I) have utility in a variety of therapeutic areas. DX-2074 at 3:1–14 (EP '756); Trial Tr. 324:20–325:17, 334:16–18 (Corbin). Those therapeutic areas include the treatment of at least a dozen specified disorders, including angina, hypertension, heart failure and atherosclerosis. DX-2074 at 3:9–14 (EP '756); Trial Tr. 324:20–325:17, 334:16–18 (Corbin).

663. EP '756 discloses that seven compounds of formula (I) are especially preferred. DX-2074 at 4:15–29 (EP '756); Trial Tr. 326:24–327:9 (Corbin). Sildenafil is one of those

especially preferred compounds. DX-2074 at 4:20–21; Trial Tr. 328:1–329:9 (Corbin). Five of those especially preferred compounds, including sildenafil, are recited for use in the method of claim 25 of the '012 patent. DX-2074 at 4:15–29 (EP '756); DX-2001 at 10:1–33; Trial Tr. 328:1–329:9 (Corbin).

664. A POSA would have understood EP '756 to disclose that all of the compounds of formula (I), including the especially preferred compounds, are potent and selective inhibitors of both cGMP PDEs, including PDE5. DX-2074 at 3:1–4, 3:5–7, 7:6–8 (EP '756); Trial Tr. 343:25–344:21 (Corbin).

665. EP '756 teaches that the compounds of formula (I), including the especially preferred compounds, may be administered orally, in a range of 4-800 mg/day, in single or multiple doses, once or several times per day. DX-2074 at 7:23–27 (EP '756); Trial Tr. 362:8–363:7 (Corbin). That dosage range encompasses the preferred dosing regimen of 5-75 mg of compound three times per day disclosed in the '012 patent. See DX 2001 at 5:65-66 ('012 patent).

666. By June 9, 1993, a POSA would have known that the compounds disclosed in EP '756 are potent and selective inhibitors of cGMP PDE, including PDE5, that are useful in the treatment of at least a dozen specified disorders and that can be administered orally in a range of 4-800mg per day. Trial Tr. 343:25–344:21 (Corbin).

667. The Ellis 1992 Declaration from the prosecution history of the '534 patent discloses *in vitro* PDE inhibitory data for 20 compounds that are encompassed by formula (I) of EP '756. DX-2004 at 55–58 ('534 patent); DX-2240 at 4 (Ellis Declaration); Trial Tr. 329:16–333:4 (Corbin).

668. Those 20 tested compounds include sildenafil, which is Example 12. DX-2240 at 4 (Ellis Declaration); Trial Tr. 331:3–24 (Corbin).

669. The Ellis 1992 Declaration discloses the following inhibitory data for sildenafil:

Example	IC_{50} (nM) or % activity at 10^{-4} M		Selectivity Ratio
	cGMP	cAMP	
12 (sildenafil)	3.6	65,000	18,056

DX-2240 at 4 (Ellis Declaration); DX-2004 at Example 12; Trial Tr. 331:14–332:16 (Corbin).

670. A POSA would have understood the Ellis 1992 Declaration to teach that the 20 tested compounds, including sildenafil, are highly potent inhibitors of PDE5, have little to no potency for inhibition of PDE3, and are highly selective for inhibition of PDE5 over PDE3. DX-2240 at 4 (Ellis Declaration); Trial Tr. 331:14–332:25 (Corbin).

671. A POSA would have recognized from the IC_{50} data in the Ellis 1992 Declaration that most of the 20 tested compounds, including sildenafil and the other especially preferred compounds, are about 100 times more potent against PDE5 than zaprinast. DX-2240 at 4 (Ellis Declaration); Trial Tr. 333:1–4 (Corbin).

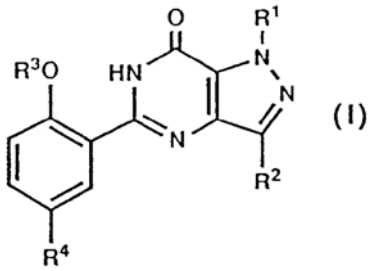
672. The ‘534 patent and its prosecution history, including the Ellis 1992 Declaration, are prior art to the ‘012 patent. Trial Tr. 330:24–331:2 (Corbin).

673. By May 13, 1994, a POSA would have known that the compounds disclosed in EP ‘756 are highly potent and selective inhibitors of PDE5 that are useful in the treatment of at least a dozen specified disorders and that those compounds can be administered orally in an amount that would be effective to treat ED. DX-2074 at 3:1–4, 3:5–7, 7:6–8 (EP ‘756); DX-2240 at 4 (Ellis Declaration); Trial Tr. 343:25–344:21, 348:21–349:15, 357:23–358:23 (Corbin).

(c) EP ‘004 (DX 2006)

674. EP ‘004 published on February 3, 1993 and is prior art to the ‘012 patent. DX-2006 at cover, at (43) (EP ‘004); Trial Tr. 333:12–18 (Corbin).

675. EP ‘004 discloses compounds of formula (I), set forth below:



(I)

R^1, R^2, R^3 and R^4 represent potential substituents, as set forth in EP ‘004. DX-2006 at 2:19–49 (EP ‘004).

676. Formula (I) of EP ‘004 encompasses at least millions of compounds that share a common core ring structure but whose substituents differ at R^1, R^2, R^3 and/or R^4. DX-2006 at 2:19–49 (EP ‘004); Trial Tr. 400:20–401:1 (Corbin).

677. EP ‘004 discloses that the compounds of formula (I) are potent and selective inhibitors of both cGMP PDEs, *i.e.*, PDE1 and PDE5, and that based on that inhibitory activity profile those compounds have utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis. DX-2006 at 2:1–14 (EP ‘004); Trial Tr. 322:20–323:5, 323:24–324:7, 333:12–334:18 (Corbin).

678. EP ‘004 discloses that five compounds of formula (I) are especially preferred. DX-2006 at 3:25–34 (EP ‘004); Trial Tr. 334:19–335:25 (Corbin). Four of those especially preferred compounds are recited for use in the method of claim 25 of the ‘012 patent. DX-2006 at 3:25–34 (EP ‘004); DX-2001 at 10:1–33 (‘012 patent); Trial Tr. 334:19–335:25 (Corbin).

679. EP '004 contains a table that discloses *in vitro* PDE inhibitory data for 13 compounds of formula (I):

EXAMPLE	IC_{50} (nM)		SELECTIVITY RATIO
	cGMP	cAMP	
3	2.2	86,000	39,090
4	1.8	63,000	35,000
11	4.9	57,000	11,632
14	1.0	57,000	57,000
15	3.4	75,000	22,058
16	3.7	53,000	14,324
20	3.7	59,000	15,945
25	3.4	84,000	24,705
29	5.5	84,000	15,272
30	1.4	58,000	41,428
31	3.4	56,000	16,470
32	1.4	38,000	27,142
39	5.3	54,000	10,188

DX-2006 at 26:1–35 (EP '004); Trial Tr. 336:1–337:15 (Corbin).

680. A POSA would have understood the IC_{50} data in that table to indicate that the 13 tested compounds are highly potent inhibitors of PDE5, weak inhibitors of PDE3 and, consequently, highly selective for inhibition of PDE5 over inhibition of PDE3. DX-2006 at 26:1–35 (EP '004); Trial Tr. 336:1–337:15 (Corbin).

681. A POSA would have understood EP '004 to disclose that all of the compounds of formula (I), including the especially preferred compounds, are potent and selective inhibitors of PDE5. Trial Tr. 323:24–324:7, 336:1–337:15 (Corbin).

682. A POSA would have recognized from the IC_{50} data in EP '004 that the tested compounds are about 100 times more potent against PDE5 than zaprinast. Trial Tr. 336:24–337:2 (Corbin).

683. EP ‘004 teaches that the compounds of formula (I), including the especially preferred compounds, may be administered orally, in a range of 4-800 mg/day, in single or multiple doses, once or several times per day. DX-2006 at 9:11–15 (EP ‘004); Trial Tr. 348:21–349:5 (Corbin). That dosage range encompasses the preferred dosing regimen of 5-75 mg of compound three times per day disclosed in the ‘012 patent. *See* DX 2001 at 5:65-66 (‘012 patent).

684. By June 9, 1993, a POSA would have known that the compounds disclosed in EP ‘004 are highly potent and selective cGMP PDE inhibitors that are useful in the treatment of at least a dozen specified disorders and that can be administered orally in a range of 4-800 mg per day. DX-2006 at 2:1–4, 2:5–14, 8:53–54, 9:11–15 (EP ‘004); DX-2001 at 5:65–66 (‘012 patent); Trial Tr. 333:12–337:15, 343:25–344:21 (Corbin).

(d) Claim 1 Of The ‘270 Patent

685. A POSA would have known from claim 1 of the ‘270 patent that the compounds recited for use in the method of that claim have utility in the treatment of ED. DX-2066 at 8:8–81 (‘270 patent); Trial Tr. 399:5–19 (Corbin); Trial Tr. 997:24–998:4 (Terrett). A POSA would have recognized that those compounds were disclosed in the prior art WO ‘104. DX-2068 at 1–2 (‘270 patent); Trial Tr. 384:16–385:10, 387:10–388:5 (Corbin), 985:22–986:3 (Terrett); Campbell Dep. Tr. at 153:11–153:14, 154:17–155:6.

686. Prior art WO ‘104 taught that the compounds recited for use in the method of claim 1 of the ‘270 patent have potent and selective inhibitory activity against cGMP PDEs, including PDE5. DX-2068 at 1–2, 8, 17–19 (‘270 patent); Trial Tr. 385:4–12, 387:14–388:13 (Corbin), 996:4–19 (Terrett).

687. A POSA would have recognized from WO ‘104 that the pharmacological activity of the compounds for use in the method of claim 1 of the ‘270 patent was due to their inhibitory

activity against cGMP PDEs, including PDE5, the only pharmacological activity disclosed in WO ‘104 for those compounds. DX-2068 at 1–2, 8, 17–19 (‘270 patent); Trial Tr. 385:4–12, 387:14–388:13 (Corbin).

(e) A POSA Would Have Recognized That The Compounds Disclosed In WO ‘104, EP ‘756 And EP ‘004 Have Substantially Overlapping Properties

688. A POSA would have known from WO ‘104, EP ‘756 and EP ‘004 that all of the compounds disclosed in those prior art references are potent and selective inhibitors cGMP PDEs, including PDE5, and have low or no potency or selectivity for cAMP PDEs. Trial Tr. 323:24–324:7, 336:1–337:15 (Corbin), 996:4-997:19 (Terrett); Terrett Dep. Tr. at 50:22-51:4, 81:25-90:5.

689. A POSA would have believed from the PDE inhibitory activity data in WO ‘104, the Ellis 1992 Declaration and EP ‘004 that all of the compounds disclosed in WO ‘104, EP ‘756 and EP ‘004 are potent and selective inhibitors of PDE5, and have little or no potency or selectivity for cAMP PDEs. Trial Tr. 323:24–324:7, 336:1–337:15, 388:6–13 (Corbin).

690. A POSA would have known that the compounds disclosed in WO ‘104, EP ‘756 and EP ‘004 would, as a consequence of their selective cGMP PDE inhibitory profiles, elevate cGMP levels, and in turn give rise to beneficial platelet anti-aggregatory, anti-vasospastic and vasodilatory activity, and potentiate the effects of EDRF (nitric oxide) and nitrovasodilators. Trial Tr. 323:24–324:7, 336:1–337:15, 384:16–385:10, 388:6–24 (Corbin); Terrett Dep Tr. at 996:9–997:19; Compare DX 2068 at 1 (WO ‘104), DX 2074 at 3:5-9 (EP ‘756) and DX 2006 at 2:5-9 (EP ‘004):

WO ‘104 (DX 2068 at 1)

The compounds of the invention exhibit selectivity for inhibition of cGMP PDEs rather than cyclic adenosine 3',5'-monophosphate phospodiesterases (cAMP PDEs) and, as a consequence of this selective PDE inhibition, cGMP levels are elevated, which in turn can give rise to beneficial anti-platelet, anti-neutrophil, anti-vasospastic and vasodilatory activity, as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF) and nitrovasodilators. Thus the

EP ‘756 (DX 2074 at 3:5-9)

The compounds of the invention exhibit selectivity for inhibition of cGMP PDEs rather than cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs) and, as a consequence of this selective PDE inhibition, cGMP levels are elevated, which in turn can give rise to beneficial platelet anti-aggregatory, anti-vasospastic and vasodilatory activity, as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF) and nitrovasodilators. Thus the compounds have utility in the treatment of a number

EP ‘004 (DX 2006 at 2:5-9)

The compounds of the invention exhibit selectivity for inhibition of cGMP PDEs rather than cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs) and, as a consequence of this selective PDE inhibition, cGMP levels are elevated, which in turn can give rise to beneficial anti-platelet, anti-neutrophil, anti-vasospastic and vasodilatory activity, as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF) and nitrovasodilators. Thus the compounds have utility in the treatment of a number of disorders,

691. A POSA would have known that the compounds disclosed in WO ‘104, EP ‘756 and EP ‘004 would, as a consequence of their selective cGMP PDE inhibitory profiles, have utility in the treatment of a number of disorders, including angina, hypertension, congestive heart failure and atherosclerosis. Trial Tr. 323:24–324:7, 336:1–337:15, 384:16–385:10, 388:6–24 (Corbin); compare DX 2068 at 1 (WO ‘104), DX 2074 at 3:9-14 (EP ‘756) and DX 2006 at 2:5-9 (EP ‘004):

WO ‘104 (DX 2068 at 1)

relaxing factor (EDRF) and nitrovasodilators. Thus the compounds have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

EP ‘756 (DX-2074 at 3:9–14)

relaxing factor (EDRF) and nitrovasodilators. Thus the compounds have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

EP ‘004 (DX-2006 at 2:5–9)

tor (EDRF) and nitrovasodilators. Thus the compounds have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

692. A POSA would have known from claim 1 of the ‘270 patent that the compounds disclosed in WO ‘104 would have utility in the treatment of ED. Trial Tr. 399:5-19, 997:24–998:4 (Terrett); Terrett Dep. Tr. at 50:22-51:9, 89:25-90:5.

693. A POSA would have known from WO ‘104, EP ‘756 and EP ‘004 that all of the compounds disclosed in those prior art references can be administered orally, in a range of 4-800 mg/day, in single or multiple doses, once or several times per day. Trial Tr. 348:21-349:5,

362:8-363:7, 388:6-23 (Corbin), 996:20–24, 997:19–23 (Terrett). Compare DX 2068 at 8-9, DX 2074 at 7:23-32 (EP '756) and DX 2006 at 9:11-20 (EP '004); Terrett Dep. Tr. at 89:25-90:9.

WO '104 (DX 2068 at 8-9)

For administration to man in the curative or prophylactic treatment of angina, hypertension or congestive heart failure, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal or sublingual administration will typically be within the range of from 1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

EP '756 (DX 2074 at 3:9-14)

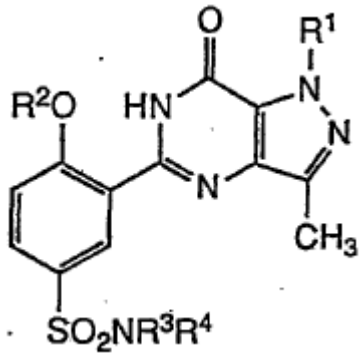
For administration to man in the curative or prophylactic treatment of angina, hypertension or congestive heart failure, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal or sublingual administration will typically be within the range of from 1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

EP ‘004 (DX 2006 at 9:11-20)

For administration to man in the curative or prophylactic treatment of angina, hypertension or congestive heart failure, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal or sublingual administration will typically be within the range of from 1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

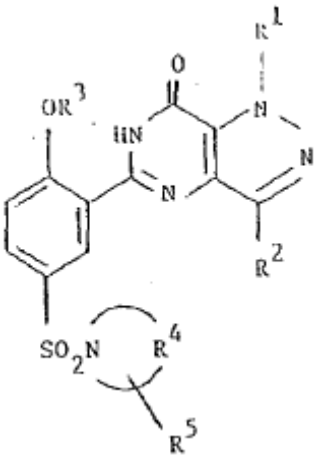
694. The compounds disclosed in WO ‘104, EP ‘756 and EP ‘004 have the following general formulas:

WO ‘104 compounds



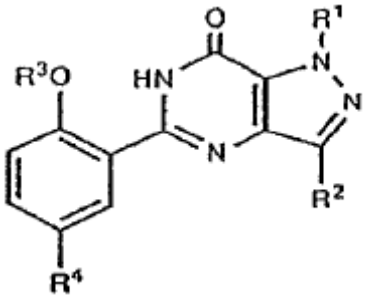
(DX-2068 at 2)

EP ‘756 compounds



(DX-2074 at 3:19–35)

EP ‘004 compounds



(DX-2006 at 2:19–30)

695. A POSA would have known that the broad range of compounds recited for use in the method of claim 1 of the ‘012 patent – *i.e.*, the compounds disclosed in EP ‘756 and EP ‘004 – belong to a structural class of compounds having an invariant pyrazolopyrimidinone nucleus and an alkoxy phenyl substituent at the 2-position. Terrett Depo Tr. at 49:18–22, 50:2–51:11. Those are compounds are 5-(2’-alkoxyphenyl)pyrazolo[4,3-d]pyrimidin-7-ones. DX-2060 at 1823.

696. All of the compounds disclosed in WO ‘104, EP ‘756 and EP ‘004 belong to the same structural class of 5-(2’-alkoxyphenyl)pyrazolo[4,3-d]pyrimidin-7-ones because they all have the same pyrazolopyrimidinone nucleus and an alkoxy substituent at the 2-position of the phenyl ring. DX-2068 at 2 (WO ‘104); DX-2074 at 3:19–35 (EP ‘756); DX-2006 at 2:19–30 (EP ‘004).

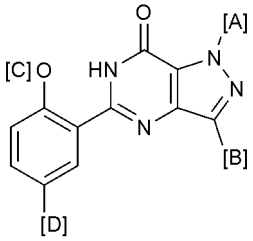
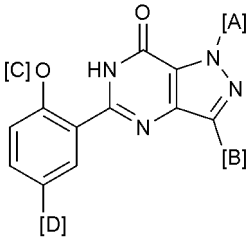
697. WO ‘104 states:

> It has now been discovered that 1,3-dialkyl-5-(disubstituted phenyl)-1,6-dihydro-7H-pyrazolo[4,3d]pyrimidin-7-ones, in which the two phenyl substituents are in a 2,5 relative disposition, possess unexpectedly high levels of both cGMP PDE inhibitory potency and, as stated above, selectivity for inhibition of cGMP PDEs over that of cAMP PDEs.

DX-2068 at 2 (WO ‘104); Trial Tr. 388:6–13 (Corbin).

698. The compounds of WO ‘104, the compounds of EP ‘756 (including sildenafil), and the compounds of EP ‘004 are 1,3-dialkyl-5-(disubstituted phenyl)-1,6-dihydro-7H-pyrazolo[4,3d]pyrimidin-7-ones, in which the two phenyl substituents are in a 2,5 relative disposition. DX-2068 at 2 (WO ‘104); DX-2074 at 3:19–35 (EP ‘756); DX-2006 at 2:19–30 (EP ‘004). WO ‘104 states that such compounds possess high levels of both cGMP PDE inhibitory potency and selectivity for inhibition of cGMP PDEs over that of cAMP PDEs. DX-2068 at 2 (WO ‘104); DX-2074 at 3:19–35 (EP ‘756); DX-2006 at 2:19–30 (EP ‘004).

699. A POSA would have had the following knowledge about the compounds recited for use in methods of claim 1 of the '270 patent and claims 25 and 26 of the '012 patent:

Compounds Recited For Use In Method Of Claim 1 Of The '270 Patent (as taught by WO '104 (DX 2068) and claim 1 of the '270 patent (DX 2066))	Compounds Recited For Use In Methods Of Claim 25 And 26 Of The '012 Patent (as taught by EP '756 (DX 2074) and EP '004 (DX 2006))
compounds having the general structure:  DX-2068 at 2	compounds having the general structure:  DX-2074 at 3:14–49; DX-2006 at 2:19–49
Potent and selective inhibitors of both PDE1 and PDE5 DX 2068 at 1, 2, 8, 17–19; Trial Tr. 338:1-339:2, 341:13–343:4 (Corbin)	Potent and selective inhibitors of both PDE1 and PDE5 DX 2074 at 3:1–7, 7:6–8; DX 2240 at 4 (Ellis 1992 Declaration); DX 2006 at 2:1–7, 8:53–54, 26:1–35; Trial Tr. 324:20–325:24, 333:19–334:18 (Corbin)
Highly potent for inhibition of PDE5. Approximately 100 times more potent than zaprinast against PDE5. DX 2068 at 17–19; Trial Tr. 341:13-343:4 (Corbin)	Highly potent for inhibition of PDE5. Approximately 100 times more potent than zaprinast against PDE5. DX 2240 at 4 (Ellis 1992 Declaration); DX 2006 at 26:1–35; Trial Tr. 331:14–333:4, 336:1–337:2 (Corbin)

Compounds Recited For Use In Method Of Claim 1 Of The '270 Patent (as taught by WO '104 (DX 2068) and claim 1 of the '270 patent (DX 2066))	Compounds Recited For Use In Methods Of Claim 25 And 26 Of The '012 Patent (as taught by EP '756 (DX 2074) and EP '004 (DX 2006))
Have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, and diseases characterized by disorders of gut motility (*e.g.*, irritable bowel syndrome). DX 2068 at 1; Trial Tr. 388:14–24, 393:25–394:25 (Corbin)	Have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency (*e.g.*, post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, and diseases characterized by disorders of gut motility (*e.g.*, irritable bowel syndrome). DX 2074 at 3:1–14; DX 2006 at 2:1–14; Trial Tr. 324:18–325:20, 393:25–394:25 (Corbin)
Orally administrable in a range of 4-800 mg/day, in single or multiple doses, once or several times per day in the treatment of angina, hypertension or congestive heart failure. Also administrable buccally, sublingually or parenterally (*e.g.*, injected intravenously, intramuscularly, subcutaneously or intracoronarily). DX 2068 at 8–9; Trial Tr. 388:6–23, 395:1–397:10 (Corbin)	Orally administrable in a range of 4-800 mg/day, in single or multiple doses, once or several times per day in the treatment of angina, hypertension or congestive heart failure. Also administrable buccally, sublingually or parenterally (*e.g.*, injected intravenously, intramuscularly, subcutaneously or intracoronarily). DX 2074 at 7:23–27; DX 2006 at 2:1–14; Trial Tr. 395:1–397:10 (Corbin)
Have utility in the treatment of ED (DX-2066 at 8:8–31)	

3. The Oral Administration Limitation In Claims 25 And 26 Of The '012 Patent Does Not Render Those Claims Patentably Distinct From Claim 1 Of The '270 Patent

700. Claims 25 and 26 of the '012 patent require oral administration of an effective amount of a compound. DX-2001 at 10:1–39 ('012 patent).

701. Claim 1 of the ‘270 patent recites administration of an “effective amount” of a compound, without regard to the route of administration. DX 2066 at 8:8–31 (‘270 patent); Trial Tr. 389:24–390:9 (Corbin). A POSA, however, would have known that claim 1 of the ‘270 patent encompassed oral administration. Trial Tr. 389:24–390:14 (Corbin). To determine the acceptable route or routes of administration encompassed by claim 1 of the ‘270 patent, a POSA would have needed to refer to the specification of the ‘270 patent. Trial Tr. 390:5–391:4 (Corbin). The specification of the ‘270 patent states that “the [disclosed] compounds may be administered orally” (DX 2066 at 1:66-67 (‘270 patent)) and discloses that oral administration is the preferred route. (DX 2066 at 7:22–26 (‘270 patent)); Trial Tr. 390:15–391:4. A POSA therefore would have known that the method of claim 1 of the ‘270 patent encompassed oral administration. Trial Tr. 389:24–391:4.

702. A POSA would have known that compared to other routes of administration, oral administration generally is more convenient, safer and enhances patient compliance. Trial Tr. 215:22–216:10; Terrett Dep. Tr. at 73:4-7.

703. A POSA would have known that because of the advantages associated with oral administration, ED investigators were actively searching for compounds that could be administered orally for the treatment of ED. Trial Tr. 215:22–216:10, 217:12–218:5 (Carson).

704. A POSA would have known from WO ‘104 that the compounds recited for use in the method of claim 1 of the ‘270 patent are potent and selective PDE5 inhibitors that could be administered orally for the treatment of a number of conditions in a dosage range of 4–800 mg per day. DX-2068 at 8–9 (WO ‘104); Trial Tr. 399:5–19 (Corbin). That dosage range would effectively treat ED. DX-2068 at 8–9 (WO ‘104); DX-2066 at 7:25–26 (‘270 patent).

705. A POSA would have known from EP '756 and EP '004 that the compounds recited for use in the methods of claims 25 and 26 of the '012 patent are potent and selective PDE5 inhibitors that could be administered orally for the treatment of the same conditions as the compounds of WO '104 at the same dosage range as disclosed for the compounds of WO '104. DX-2074 at 3:1–14, 7:6–8, 7:23–27 (EP '756); DX 2006 at 2:1-14, 8:53-54, 9:11-15 (EP '004); DX 2068 at 1, 8-9 (WO '104); Trial Tr. 368:14–369:18, 398:24–399:19 (Corbin).

706. Even though ED is not one of conditions specified in EP '756 or EP '004, a POSA would have no reason to think that the compounds of EP '756 and EP '004, which reach other organs in the body via the bloodstream, would not reach the smooth muscle tissues of the penis. Trial Tr. 218:6–219:2 (Carson), 368:14–369:18 (Corbin).

707. A POSA reasonably would have expected that the oral administration of a potent and selective PDE5 inhibitor would be effective in targeting the erectile tissue in the penis because of PDE5's limited tissue distribution and its unique substrate specificity for cGMP. DX 2074 at 7:23-25 (EP '756); DX 2006 at 9:11-24 (EP '004), Trial Tr. 218:6-219:2, 219:25-220:11 (Carson), 367:19-368:10 (Corbin).

708. A POSA would have known of the teachings of Murray 1993 and would reasonably have expected that a potent and selective PDE5 inhibitor would have a narrow range of physiological and pharmacological actions and would have its greatest effect in tissues in which there is a high level of guanylate cyclase activity, such as the corpus cavernosum. DX 2138A at 151, 155 (Murray 1993); Trial Tr. 316:23-318:18, 320:25-321:13 (Corbin).

709. A POSA would have known that the '445 patent (DX 2189) and the '771 patent (DX 2191) taught orally administered hypotensive (blood pressure lowering) compounds for the effective and safe treatment of ED, and taught that oral administration was a preferred route of

administration. *See supra* ¶¶ 242-263. A POSA would have known that the '771 and '445 patents claimed oral administration of those compounds for the treatment of ED. DX 2189 at claim 2 ('771 patent); DX 2191 at claims 1-5 ('445 patent); Trial Tr. 783:4-13 (Ellis), 956:17-957:17 (Goldstein).

710. During reexamination of the '012 patent, the BPAI considered the '445 patent and referred to it as Goldstein. *See* DX 2303 at 38 n.47 (February 12, 2010 BPAI Decision).

711. During reexamination of the '012 patent, the USPTO recognized that "Goldstein [*i.e.*, the '445 patent] discloses treating ED by oral, rectal, or parenteral administration of etoperidone" (DX 2303 at 40 (February 12, 2010 BPAI Decision) and that it teaches "successful treatment of ED by orally administering a drug" (DX 2303 at 41 (February 12, 2010 BPAI Decision)).

712. During reexamination of the '012 patent, the Board of Patent Appeals and Interferences found, based upon a preponderance of record, that oral administration of etopenidone is an effective ED therapy. DX 2303 at 7, 40-41 (finding of fact 91), 50 (February 12, 2010 BPAI Decision).

713. A POSA would have considered the compounds recited for use in the method of claim 1 of the 270 patent to be interchangeable with the compounds recited for use in the methods of claims 25 and 26 of the '012 patent for the purpose of treating ED by oral administration. Trial Tr. 398:24–399:19 (Corbin).

714. During the reexamination of the '012 patent, the Board of Patent Appeals and Interferences ("BPAI") considered whether claim 1 of the '270 patent rendered claim 24 of the '012 patent invalid for obviousness type patenting. DX 2303 at 55 (February 12, 2010 BPAI Decision).

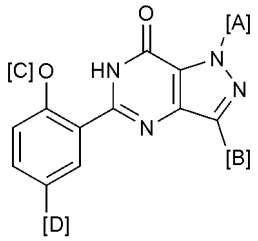
715. Claim 24 of the '012 patent claims oral administration of a PDE5 inhibitor, any PDE5 inhibitor, for the treatment of ED. DX 2001 at 9:36-41 ('012 patent).

716. The BPAI stated: "Appellant [Pfizer] argues that the prior art teaches successful treatment of ED by intracavernal injection of a drug and that the systemic effects of orally administered antihypertensives and PDE inhibitors may cause or worsen ED. However, the prior art submitted by Appellant, namely Goldstein [the '445 patent, DX 2191] and Krane, also teach successful treatment of ED by orally administering a drug." DX 2303 at 51-52 (February 12, 2010 BPAI Decision), internal citations omitted.

717. The BPAI found that claim 1 of the '270 patent rendered claim 24 of the '012 patent invalid for obviousness type double patenting despite the fact that claim 24 of the '012 patent expressly claims oral administration while claim 1 of the '270 patent does not. DX 2303 at 55 (February 12, 2010 BPAI Decision); compare DX 2001 at 9:36-41, claim 24 ('012 patent) and DX 2066 at 8:8-10, claim 1 ('270 patent).

4. The Structural Differences Between The Compounds Do Not Render The Claimed Methods Of Treating ED Patentably Distinct

718. The compounds recited for use in the methods of claim 1 of the '270 patent and claims 25 and 26 of the '012 patent all have the following general structure:



Compare DX-2068 at 2 (WO '104), DX-2074 at 3:19–35 ('756 patent), and DX-2006 at 2:19–30 (WPO '004).

719. The compounds recited for use in the methods of claim 1 of the '270 patent and claims 25 and 26 of the '012 patent share a common core ring structure, and have Substituents

[A], [B], [C] and [D] in the same positions relative to the common core ring structure. DX-2001 at 2:1–13, 10:1–39 (‘012 patent) and DX-2066 at 8:8–31 (WPO ‘004).

720. The formula recited in claim 1 of the ‘270 patent encompasses compounds that have substituents identical to those of sildenafil at Substituent [A] (methyl) and Substituent [C] (ethyl) but differ from sildenafil at Substituents [B] and [D]. Compare DX 2001 at 9:36-41, claim 24 (‘012 patent) and DX 2066 at 8:8-10, claim 1 (‘270 patent).

721. A POSA would have understood the compounds recited for use in the method of claim 1 of the ‘270 patent to be structurally similar to sildenafil because they share identical core structures and some substituents. Terrett Dep. Tr. at 50:2-51:11; Compare DX 2001 (‘012 patent) and DX 2066 (‘270 patent).

722. WO ‘104 discloses that the billions of compounds recited in claim 1 of the ‘270 patent, regardless of their substituents, are potent and selective inhibitors of PDE5, have utility in the treatment of at least a dozen specified disorders and are orally administrable in a dosage range of 4–800 mg per day. DX 2068 at 1, 2, 8, 9, 17–19 (WO ‘104); Trial Tr. 400:5-15 (Corbin).

723. A POSA would have understood that EP ‘756 and EP ‘004 disclose that the billions of compounds disclosed in those prior art references (including the especially preferred compounds, including sildenafil), regardless of their substituents, also are potent and selective inhibitors of PDE5, also have utility in the treatment of at least those same specified disorders and also are orally administrable in a dosage range of 4–800 mg per day. DX 2074 at 3:1–14, 4:15–29, 6:6–8, 7:23–27 (EP ‘756); DX 2240 at 4 (Ellis Declaration); DX 2006 at 2:1–14, 3:25–34, 8:53–54, 9:11–15, 26:1–35 (WP ‘004); Trial Tr. 398:24–401:1 (Corbin).

724. Notwithstanding any differences in substituents between the compounds, a POSA would have expected the compounds disclosed in WO ‘104 to be interchangeable with the compounds disclosed in EP ‘756 and EP ‘004 for therapeutic utilities based on PDE5 inhibition, the only pharmacological activity for those compounds disclosed in those publications. Trial Tr. 382:23–383:9, 384:10–385:10 (Corbin). In light of the overlapping chemical structures and the identical pharmacological activities (potent and selective inhibitors of PDE5), therapeutic utilities, routes of administration and dosages for use of the compounds disclosed in WO ‘104, EP ‘756 and EP ‘004, a POSA reading in claim 1 of the ‘270 patent that the compounds of WO ‘104 can be administered to a male human for the treatment of ED would also have had a reasonable expectation of successfully treating ED in humans using any of the especially preferred compounds of EP ‘756 or EP ‘004, including sildenafil. Trial Tr. 398:24–401:1, 508:16–510:7 (Corbin).

725. A POSA would have considered the compounds recited for use in the method of claim 1 of the ‘270 patent to be interchangeable with the compounds recited for use in the methods of claims 25 and 26 of the ‘012 patent for the purpose of treating ED. Trial Tr. 398:24–401:1, 508:16–510:7 (Corbin).

PROPOSED CONCLUSIONS OF LAW

I. CONTROLLING AUTHORITY AND STANDARDS OF PROOF

A. Federal Circuit Law Applies

1. Federal Circuit precedent governs matters of substantive patent law in this court. The Federal Circuit has adopted the decisions of the Court of Customs and Patent Appeals ("C.C.P.A.") as its own precedent, making those decisions binding on this court. *South Corp. v. United States*, 690 F.2d 1368, 1370 (Fed. Cir. 1982) (en banc).

B. Standards of Proof

2. Although historically about half of litigated patents are held invalid, a patent is presumed valid. 35 U.S.C. § 282. Although 35 U.S.C. § 282 does not explicitly set forth a standard of proof for overcoming the presumption of validity, the Federal Circuit has held that invalidity must be established by "clear and convincing evidence." *Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359-60 (Fed. Cir. 1984).

II. RIGHT, TITLE OR INTEREST IN OR TO THE '012 PATENT

3. Pfizer has failed to prove that Pfizer Inc. has any right, title or interest in or to the '012 patent.

4. Pfizer has failed to prove that Pfizer Limited has any right, title or interest in or to the '012 patent.

5. Pfizer has failed to prove that Pfizer Ireland Pharmaceuticals, a partnership existing pursuant to the laws of Ireland, has any right, title or interest in or to the '012 patent.

6. Pfizer has failed to prove that Pfizer Ireland Pharmaceuticals, a private unlimited liability company incorporated in Ireland, has any right, title or interest in or to the '012 patent.

7. Pfizer has failed to prove that Pfizer Ireland Pharmaceuticals, the partnership, has a valid exclusive license in the '012 patent.

8. Pfizer has failed to prove that Pfizer Ireland Pharmaceuticals, the company, has a valid exclusive license in the '012 patent.

9. Pfizer has failed to establish that any of the Pfizer plaintiffs have standing to enforce the '012 patent.

10. "The party bringing the action bears the burden of establishing that it has standing." *Sicom Sys., Ltd. v. Agilent Techs., Inc.*, 427 F.3d 971, 975–76 (Fed. Cir. 2005).

11. "It is a long-settled principle that standing cannot be inferred argumentatively from averments in the pleadings, but rather "must affirmatively appear in the record." *FW/PBS, Inc. v. City of Dallas*, 493 U.S. 215, 33 (1990).

12. "Standing to sue is a threshold requirement in every federal action." *Sicom Sys.*, 407 F.3d at 975-76. Plaintiffs must have standing at the inception of and throughout a lawsuit. *Schreiber Foods, Inc. v. Beatrice Cheese, Inc.*, 402 F.3d 1198, 1203 (Fed. Cir. 2005).

13. "The federal courts are under an independent obligation to examine their own jurisdiction, and standing is perhaps the most important of the jurisdictional doctrines." *FW/PBS, Inc.*, 493 U.S. at 230.

14. "To bring an action for patent infringement, a party must be either the patentee, a successor-in-title to the patentee, or an exclusive licensee of the patent at issue." *Fieldturf Inc. v. Southwest Recreational Indus., Inc.*, 357 F.3d 1266, 1268 (Fed. Cir. 2004).

15. A patent owner is the only entity that has standing to prosecute an action for infringement in its own name. 35 U.S.C. § 281 ("A patentee shall have remedy by civil action for infringement of his patent."). To sue for infringement, an exclusive licensee must join the

patentee. *Fieldturf*, 357 F.3d at 1268. To establish standing, "[a] purported exclusive licensee must show that he possesses all substantial rights in the patent." *Id.*

16. "A nonexclusive license confers no constitutional standing on the licensee to bring suit or even to join a suit with the patentee because a nonexclusive licensee suffers no legal injury from infringement." *Sicom*, 427 F.3d at 976.

III. THE BUSH DISSERTATION, THE '534 PATENT AND ITS PROSECUTION HISTORY ARE PRIOR ART TO THE '012 PATENT

17. The 35 U.S.C. § 102 printed publication bar states: "A person shall be entitled to a patent unless – (a) the invention was…described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or (b) the invention was…described in a printed publication in this or a foreign country…more than one year prior to the date of the application for patent in the United States…." 35 U.S.C. §§ 102(a) and (b) (2006). "The bar is grounded on the principle that once an invention is in the public domain, it is no longer patentable by anyone." *Application of Bayer*, 568 F.2d 1357, 1361 (C.C.P.A. 1978).

18. The printed publication bar is a legal determination based on issues of underlying fact, and therefore must be approached on a case-by-case basis. *In re Hall*, 781 F.2d 897, 898 (Fed. Cir. 1986).

19. "Because there are many ways in which a reference may be disseminated to the interested public, 'public accessibility' has been called the touchstone in determining whether a reference constitutes a 'printed publication' bar[.]" *Id.* at 898-99 (holding that a single cataloged doctoral thesis in one university library constituted a printed publication because it was sufficient accessibility to those interested in the art exercising reasonable diligence). "A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject

matter or art exercising reasonable diligence, can locate it." *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006); *see also In re Wyer*, 655 F.2d 221, 226 (C.C.P.A. 1981); *In re Klopfenstein*, 380 F.3d 1345, 1348 (Fed. Cir. 2004). "Evidence of routine business practice can be sufficient to prove that a reference was made accessible before a critical date." *Constant v. Ad. Micro-Devices, Inc.*, 848 F.2d 1560, 1568-69 (Fed. Cir. 1988); *see also Hall*, 781 F.2d at 899.

20. "When any claim of an application or a patent under reexamination is rejected, the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§ 1.42, 1.43, or 1.47, may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based." 37 C.F.R. § 1.131(a). "Prior invention may not be established under this section in any country other than the United States, a NAFTA country, or a WTO member country." *Id.* "Prior invention may not be established under this section before December 8, 1993, in a NAFTA country other than the United States, or before January 1, 1996, in a WTO member country other than a NAFTA country." *Id.*

A. The Bush Dissertation Is A Prior Art Printed Publication Under 35 U.S.C. § 102(a) And Therefore Is Prior Art To The '012 Patent

21. Pfizer represented in Court that the Bush Dissertation is prior art to the '012 patent for purposes of this case. Trial Tr. at

B. The '534 Patent And Its Prosecution History Are Prior Art To The '012 Patent Under 35 U.S.C. §§ 102(a)

22. The file wrapper or prosecution history of an issued patent becomes available to the public on the day that the patent issues. 37 C.F.R. § 1.11(a) (1993) ("After a parent has been issued or a statutory invention registration has been published, the specification, drawings and all papers relating to the case in the file of the patent or statutory invention registration are open to

inspection by the public, and copies may be obtained upon paying the fee therefor."); *see also* M.P.E.P. § 901.02 (8th ed., 2010) ("The information that is available to the public under 37 CFR 1.11(a) may be used as prior art under 35 U.S.C. 102(a) or 102(b) as of the date the information became publicly available.").

23. The '534 patent issued on October 5, 1993, at which time the patent and its prosecution history became available and accessible to the public.

24. The '534 patent is prior art to the '012 patent under 35 U.S.C. § 102(a).

25. The prosecution history of the '534 patent is prior art to the '012 patent.

26. Pfizer cannot submit an oath or declaration to establish invention date prior to October 5, 1993 because the activities related to the alleged invention of the subject matter claimed in claims 25 and 26 of the '012 patent that occurred prior to October 5, 1993 occurred outside of the United States.

IV. THE PRIORITY DATE OF THE '012 PATENT IS NO EARLIER THAN MAY 13, 1994

A. Priority

27. Generally, an applicant may antedate prior art by relying on the benefit of a prior filed foreign application to establish an effective date earlier than that of the reference. *See* 35 U.S.C. § 119. Under Section 119, "the claims set forth in a United States application are entitled to the benefit of a foreign priority date if the corresponding foreign application supports the claims in the manner required by Section 112, ¶ 1." *In re Gosteli*, 872 F.2d 1008, 1010 (Fed Cir. 1989). The description in the foreign application must clearly allow a POSA to recognize that the inventor invented what is claimed in the later application. *Id.* at 1012; *see also In re Ahlbrecht*, 435 F.2d 908, 911 (C.C.P.A. 1971) (parent application must have both a "written

description in full, clear, concise, and exact terms" and must "enable any person skilled in the art to make and use" the invention).

28. To claim the benefit of the filing date of an earlier filed application, that earlier filed application must satisfy the "how to use" prong of Section 112, ¶ 1. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1322–25 (Fed. Cir. 2005) ("In order to obtain a priority date earlier than June 27, 1990, Rasmusson needed to provide experimental proof that his invention could be effective in treating cancer. … Rasmusson failed to do so. … If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis.").

29. "[T]he how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention." *Id*. at 1323 (internal quotations and citations omitted).

30. "An applicant's failure to disclose how to use an invention may support a rejection under either section 112, paragraph 1 for lack of enablement, or section 101 for lack of utility when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention." *Id*. (internal quotations and citations omitted); *see also id*. ("Where there is no indication that one skilled in the art would accept without question statements as to the effects of the claimed drug products and no evidence has been presented to demonstrate that the claimed products do have those effects, an applicant has failed to

demonstrate sufficient utility and therefore cannot establish enablement.") (internal quotations and citations omitted).

31. The patentee has the burden of showing why the written description in the earlier application supports the claim, and that the prior art is not prior art because the asserted claim is entitled to the benefit of the earlier filing date. *Tech. Licensing Corp. v. VideoTek*, 545 F.3d 1316, 1327, 1329 (Fed. Cir. 2008); *see Research Corp. Techs., Inc. v. Microsoft Corp.,* 627 F.3d 859, 870 (Fed. Cir. 2010) ("The challenger has the burden of going forward with invalidating prior art. The patentee then has the burden of going forward with evidence to the contrary, *i.e.*, the patentee must show that the prior art does not actually invalidate the patent or that it is not prior art because the asserted claim is entitled to the benefit of an earlier filing date.") (citing *Tech. Licensing*, 545 F.3d at 1327, 1329).

32. To comply with the written description requirement of 35 U.S.C. § 112, ¶ 1, the patent disclosure must convey with reasonable clarity to a POSA that the inventor was in possession of the claimed invention at the time of the application. *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*); *see also LizardTech, Inc. v. Earth Resources Mapping, Inc*., 424 F.3d 1336, 1344-45 (Fed. Cir. 2005).

33. The written description test "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Ariad*, 598 F.3d at 1351. In other words, one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims. *Purdue Pharma. L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). A determination that a patent is invalid for failure to meet the written description requirement is a question of fact. *Ariad*, 598 F.3d at 1355.

34. Written description is not a question of whether a POSA might be able to construct the patentee's invention from the teachings of the disclosure; rather, it is a question of whether the application "necessarily discloses" the particular invention. *See Purdue Pharma.*, 230 F.3d at 1327 (quoting *Martin v. Mayer*, 823 F.2d 500, 505 (Fed. Cir. 1987)). "[A] description that merely renders the invention obvious does not satisfy the requirement." *Ariad*, 598 F.3d at 1352.

35. The invention must appear in the specification with all of its claimed features to comply with the written description requirement. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The patentee does not gain the benefit of the filing date of an earlier application unless each application in the chain leading back to the earlier application describes the invention with all of its claimed features. *Id.* at 1571-72.

36. Courts require, pursuant to 35 U.S.C. § 112, that a patent disclosure enable a POSA to make and use the full scope of claimed subject matter without undue experimentation. *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003); *Monsanto Co. v. Syngenta Seeds, Inc.*, 431 F. Supp. 2d 482, 488 (D. Del. 2006), *aff'd*, 503 F.3d 1352 (Fed. Cir. 2007). The Federal Circuit has explained that "as part of the *quid pro quo* of the patent bargain, the applicant's specification must enable one of ordinary skill in the art to practice the full scope of the invention." *AK Steel*, 344 F.3d at 1244. If the scope of a claim exceeds the scope of enablement then the claim is invalid. *Monsanto*, 431 F. Supp. 2d at 488.

B. **GB '920 Does Not Support The Asserted Claims Of The '012 Patent**

37. Teva has presented the Bush Dissertation, the '534 patent and the prosecution history of the '534 patent as invalidating prior art to the '012 patent under 35 U.S.C. § 102(a). Pfizer has the burden of going forward with evidence that those references are not prior art

because the asserted claims are entitled to the benefit of an earlier filing date. *Tech Licensing Corp.*, 545 F.3d at 1327; *Research Corp. Techs.*, 627 F.3d a 870.

38. GB '920 fails to support the asserted method claims of the '012 patent in a manner sufficient to entitle those claims to the benefit of the June 9, 1993 filing date of GB '920.

39. Claim 25 of the '012 patent is not entitled to the benefit of the June 9, 1993 filing date of GB '920.

40. Claim 26 of the '012 patent is not entitled to the benefit of the June 9, 1993 filing date of GB '920.

V. CLAIMS 25 AND 26 OF THE '012 PATENT ARE OBVIOUS UNDER 35 U.S.C. § 103

A. Obviousness

41. A claim is obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). The factual inquiries in an obviousness analysis (the *Graham* factors) are: "(1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations, if any, of non-obviousness." *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1368 (Fed. Cir. 2003).

42. The first three *Graham* factors establish a *prima facie* case of obviousness. *In re Mayne*, 104 F.3d 1339, 1341-42 (Fed. Cir. 1997), *citing Miles Labs., Inc. v. Shandon Inc.*, 997 F.2d 870, 877 (Fed. Cir. 1993).

43. Obviousness is a legal conclusion that is based on an analysis of the factual inquiries in the first three *Graham* factors. *McNeill-PPC*, 337 F.3d at 1368; *Newell Cos. v. Kenney Mfg. Co.*, 864 F.2d 757, 767 (Fed. Cir. 1988).

44. The clear and convincing evidence standard does not apply to the "ultimate legal conclusion of obviousness itself," but only to the disputed facts underlying the conclusion of obviousness. *Newell Cos.*, 864 F.2d at 767.

45. In evaluating obviousness, a court should consider whether the invention is more than a predictable use of prior art elements according to their established functions, and whether it does more than yield predictable results. *Monolithic Power Sys., Inc. v. O2 Micro Int'l Ltd.*, 558 F.3d 1341, 1352 (Fed. Cir. 2009); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

46. To determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue, a court can look to interrelated teachings of multiple patents, the effects of demands known to the design community or present in the marketplace, and the background knowledge possessed by a POSA. *KSR*, 550 U.S. at 417-18. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. *Id.* at 417. Although an obviousness analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, a court can take account of the inferences and creative steps that a POSA would employ. *Id.* at 417-18.

47. Obvious variants of prior art references are considered part of the public domain. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007).

48. When the prior art provides the means of making the invention and predicts the results, and the patentee merely verifies the expectation through "routine testing," the claims are obvious. *Pfizer, Inc. v. Apotex*, 480 F.3d 1348, 1367 (Fed. Cir. 2007). Moreover, "only a reasonable expectation of success, *not a guarantee*, is needed" to show obviousness. *Id.* at 1364 (emphasis added).

49. "Even if a reference discloses an inoperative device, it is prior art for all that it teaches." *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989). Therefore, "a non-enabling reference may qualify as prior art for the purpose of determining obviousness under [35 U.S.C.] 103." *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed. Cir. 1991).

50. If each individual element of a claim is disclosed in the prior art, the patentee must show that the combination claimed represents an unobvious step over the prior art, by demonstrating that it was uniquely challenging or difficult for a POSA. *See Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007); *see also Ex parte Catan*, 83 U.S.P.Q.2d 1569, 1575 (B.P.A.I. 2007) (holding that a patentee must provide evidence that the claim yielded "an unexpected result or was beyond the skill of one having ordinary skill in the art").

B. **Claims 25 And 26 Of The '012 Patent Are Invalid Under 35 U.S.C. § 103**

51. Claim 25 of the '012 patent is invalid under 35 U.S.C. § 103.

52. Claim 26 of the '012 patent is invalid under 35 U.S.C. § 103

53. During reexamination of the '012 patent, the Examiner applied an improperly rigid standard for obviousness.

54. Had the Examiner applied the less rigid *KSR* standard, claims 25 and 26 of the '012 patent would not have been allowed.

1. **Claims 25 And 26 Of The '012 Patent Are Obvious Over Rajfer 1992, Murray 1993 Or The Bush Dissertation, In View Of EP '756 And/Or EP '004 And The General State Of The Art**

55. Claim 25 of the '012 patent is *prima facie* obvious over Rajfer 1992 in view of EP '756, EP '004 and the general state of the art.

56. Claim 26 of the ‘012 patent is *prima facie* obvious over Rajfer 1992 in view of EP ‘756 and the general state of the art.

57. Claim 25 of the ‘012 patent is *prima facie* obvious over Murray 1993 in view of EP ‘756, EP ‘004 and the general state of the art.

58. Claim 26 of the ‘012 patent is *prima facie* obvious over Murray 1993 in view of EP ‘756 and the general state of the art.

59. Claim 25 of the ‘012 patent is *prima facie* obvious over the Bush Dissertation in view of EP ‘756, EP ‘004 and the general state of the art.

60. Claim 26 of the ‘012 patent is *prima facie* obvious over the Bush Dissertation in view of EP ‘756 and the general state of the art.

2. Claims 25 And 26 Of The ‘012 Patent Are Obvious Over EP ‘756 And/Or The ‘534 Patent In View Of The General State Of The Art

61. Claim 25 of the ‘012 patent is *prima facie* obvious over EP ‘756 in view of the general state of the art.

62. Claim 26 of the ‘012 patent is *prima facie* obvious over EP ‘756 in view of the general state of the art.

63. Claim 25 of the ‘012 patent is *prima facie* obvious over the ‘534 patent in view of the general state of the art.

64. Claim 26 of the ‘012 patent is *prima facie* obvious over the ‘534 patent in view of the general state of the art.

C. Secondary Considerations Do Not Favor A Finding Of Non-Obviousness

1. Background Law On Secondary Considerations

65. Plaintiffs bear the burden of presenting evidence, if any exists, to rebut Teva’s strong *prima facie* showing that the claimed invention would have been obvious to a POSA.

Wyers v. Master Lock Co., 616 F.3d 1231, 1245-46 (Fed. Cir. 2010); *In re GPAC, Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995); *In re Dillon*, 919 F.2d 688, 692-93 (Fed Cir. 1990) (en banc) (where the Board of Patent Appeals and Interferences presented a *prima facie* case of obviousness, it fell to the patent applicant to rebut that case by showing "unexpectedly improved properties…or any other argument or presentation of evidence that is pertinent"); *Newell Cos., Inc. v. Kenney Mfg. Cos.*, 864 F.2d 757, 768-69 (Fed. Cir. 1988).

66. To attempt to rebut Teva's strong *prima facie* showing of obviousness, plaintiffs may offer evidence of so called "secondary considerations" of non-obviousness, including the failure of others to make the claimed invention, unexpected results, skepticism by others that the claimed invention could work, and commercial success attributable to the merits of the claimed invention. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

67. It is a question of law whether Plaintiffs' evidence of secondary considerations is sufficient to rebut Teva's *prima facie* case of obviousness. *See Wyers*, 616 F.3d at 1246.

68. It is well established that secondary considerations will not save a patent when the prior art provides "strong evidence of obviousness." *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1131 (Fed. Cir. 2000). Secondary considerations are not a significant factor where the record establishes a strong *prima facie* case of obviousness, such as Teva's evidence of obviousness. *Leapfrog*, 485 F.3d at 1162 (even though patentee "provided substantial evidence of commercial success, praise, and long-felt need…the evidence on secondary considerations was inadequate to overcome" the strong case of obviousness presented by the accused infringer). *See also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007); *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006); *Sandt Tech., Ltd. v. Resco Metal and Plastics Corp.*, 264 F.3d 1344, 1355 (Fed. Cir. 2001); *In re*

GPAC, Inc., 57 F.3d 1573, 1580-81 (Fed. Cir. 1995); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 315-17 (Fed. Cir. 1985).

69. In obviousness cases, secondary considerations do not control. *Pfizer*, 480 F.3d at 1372; *Newell*, 864 F.2d at 768-69 ("although these factors must be considered, they do not control the obviousness conclusion").

70. A plaintiff's mere presentation of evidence of secondary considerations is not enough to override a finding of obviousness; the Court must consider the totality of the evidence in determining obviousness. *See Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483-84 (Fed. Cir. 1997).

2. The Totality Of The Evidence Indicates That Claims 25 And 26 Of The '012 Patent Have No Nexus To Any Asserted Secondary Consideration

71. Part of the totality of the evidence that the Court must consider is evidence of a nexus, or a lack thereof, between the subject matter of claims 25 and 26 of the '012 patent and any asserted secondary considerations. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006) ("Evidence of commercial success, or other secondary considerations, is only significant if there is a nexus between the claimed invention and the commercial success."); *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327 (Fed. Cir. 2008) (explaining that the patentee must show a "nexus between the merits of the claimed invention and evidence of secondary considerations…in order for the evidence to be given substantial weight in an obviousness decision" (quotation marks omitted)).

72. The patentee must present specific evidence showing nexus; an opinion is not enough. *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) ("Huang's affidavit contains a conclusory assertion that, in his opinion, the sales of the grips derive from the increased thickness of the polyurethane layer and the alignment of the pores. This merely represents the

inventor's opinion as to the purchaser's reason for buying the product, and, alone, is insufficient. Instead, the applicant must submit some factual evidence that demonstrates the nexus between the sales and the claimed invention-for example, an affidavit from the purchaser explaining that the product was purchased due to the claimed features.").

73. To prove that a nexus exists, the patentee must present evidence sufficient to prove a direct connection between the asserted secondary consideration and the inventive contribution of the claimed features as recited in the language of the patent claims. *King Pharm., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1280-81 (Fed. Cir. 2010) ("King has not shown any nexus between the drug's alleged commercial success and the specific invention claimed"); *In re DBC*, 545 F.3d 1373, 1384 (Fed. Cir. 2008) ("the evidence does not reveal in any way that the driving force behind those sales [of the nutraceutical at issue] was the claimed combination of mangosteen fruit, mangosteen rind extract, and fruit or vegetable juice."); *Ormco*, 463 F.3d at 1311-12 ("if the feature that creates the commercial success was known in the prior art, the success is not pertinent"); *see also B.E. Meyers & Co. v. United States*, 47 Fed. Cl. 375, 378-79 (Fed. Cl. 2000) (finding that "[d]espite this definitional elasticity, plaintiff fails to provide any specific examples of a direct connection between its know-how, improvements, and manufacturing processes, and the claimed features of its invention as embodied in the language of the particular patent claims it alleges were infringed").

74. If no nexus is proven, the Court should not attribute substantial weight to secondary considerations, such as commercial success: "[a] nexus between the merits of the claimed invention and evidence of secondary considerations is required in order for the evidence to be given substantial weight in an obviousness decision." *Muniauction*, 532 F.3d at 1327-28 (citations omitted and emphasis added); *GPAC*, 57 F.3d at 1580 (with respect to secondary

considerations of nonobviousness, the "proponent must establish a nexus between the evidence and the merits of the claimed invention"); *Ormco*, 463 F.3d at 1311-12 ("evidence of commercial success, or other secondary considerations, is only significant if there is a nexus between the claimed invention and the commercial success").

75. It is possible for a product to embody the patent claims, and yet for the sales of the product to lack a nexus to the patent claims. *DBC*, 545 F.3d at 1376, 1383-84 (no nexus established where the patent claims covered a "nutraceutical composition[ ] comprising a mixture of the pulp and pericarp of the mangosteen fruit" because despite "$130 million in sales in two years," those sales may have been "due to other factors-for example, the increasing popularity of the mangosteen fruit in general").

3. The Court Should Give No Weight To Any Of The Secondary Considerations

76. Secondary considerations are not sufficient to overcome Teva's strong *prima facie* showing of obviousness of claims 25 and 26 of the '012 patent.

(a) The Alleged Commercial Success Of Viagra® Is Not An Indicator Of Non-Obviousness Of Claims 25 And 26 Of The '012 Patent

77. "[T]he secondary consideration of commercial success exists largely to provide a means for patentees to show in close cases that subject matter that appears obvious in law is unobvious because a high degree of commercial success permits the inference that others have tried and failed to reach a solution." *Syntex LLC v. Apotex, Inc.*, 407 F.3d 1371, 1383 (Fed. Cir. 2005). This is not a close case; regardless, the sales and profits of Viagra® do not indicate that claims 25 and 26 are not obvious.

78. Before a patent owner may rely on evidence of commercial success to support the patentability of a claim, the owner must establish a nexus between the claim and the success. *In*

re Mettke, 570 F.3d 1356, 1361 (Fed. Cir. 2009) (affirming a finding of obviousness when the patentee "failed to meet his burden because he has not shown that the alleged commercial success is due to the claimed invention."), *reh'g denied* (Aug. 17, 2009); *Sandt Tech., Ltd. v. Resco Metal and Plastics Corp*., 264 F.3d 1344, 1355 (Fed. Cir. 2001) ("[N]exus was not proven between [a] patented feature and the [patent owner's] substantial sales.").

79. To show nexus, the patentee "must offer proof 'that the sales were a direct result of the unique characteristics of the claimed invention – as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter.'" *DBC*, 545 F.3d at 1384 (quoting *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) ("[T]he applicant must submit some factual evidence that demonstrates the nexus between the sales and the claimed invention")).

80. A nexus between the patented invention and commercial success is lacking if the success cannot be linked to patentable features of the claimed invention. *Asyst Tech., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008).

i. There Is No Nexus Between Claims 25 and 26 of The '012 Patent and Viagra®'s Sales Because The '534 Patent Blocked Others From Practicing The Subject Matter In The Asserted Claims

81. Commercial success has "minimal probative value" in cases where "others were legally barred from commercially testing" the prior art. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005). Similarly, there can be no nexus where the public did not know about the prior art until after the claimed subject matter was first filed. *See Procter & Gamble v. Teva Pharms. USA*, 566 F.3d 989, 998 n.2 (Fed. Cir. 2009).

82. In some cases, "[c]ommercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had

the idea been obvious to persons skilled in the art. Thus, the law deems evidence of (1) commercial success, and (2) some causal relation or 'nexus' between an invention and commercial success of a product embodying that invention, probative of whether an invention was non-obvious." *Merck & Co.*, 395 F.3d at 1376.

83. In *Senju Pharm. Co. Ltd. v. Apotex Inc*., 717 F. Supp. 2d 404 (D. Del. 2010), the defendant owned a prior patent claiming the compound gatifloxacin, and the patent-in-suit claimed compositions and methods incorporating the compound. *Id.* at 408, 426. The defendants argued that "others were legally barred from testing gatifloxacin products," like the ones claimed in the patent-in-suit, until the compound patent expired and therefore "the court may not find an inference of nonobviousness with respect to any alleged commercial success of ZYMAR®," the alleged commercial embodiment of the patent-in-suit. *Id.* at 426. The Court, "[c]onsistent with the Federal Circuit's holding that an inference of nonobviousness is weakened in such context," gave "minimal probative value" to plaintiffs' commercial success argument. *Id.*

84. In *Procter & Gamble*, the Federal Circuit held that "[t]he [lower] court rightly gave little weight to risedronate's commercial success because the prior art '406 patent was also assigned to P&G. As of December 6, 1985, the filing date of the '122 patent, 2-pyr EHDP could be found only in a pending application for the '406 patent, which was not available to the public." 566 F.3d at 998 n.2.

ii. There Is No Nexus To Claims 25 And 26 Of The '012 Patent Because A Separate "Blocking" Patent Covers The Compound Sildenafil And Its Properties

85. If there are multiple patents covering one commercialized product, the patentee must clearly relate the commercial success to the patentable features in each patent. *Am. Std., Inc. v. York Int'l Corp.*, 244 F. Supp. 2d 990, 996 (W.D. Wis. 2002) ("Testimony given

addressed the benefits of both the '560 and '190 patents, and did not show the '190 patent contributing significantly by itself to plaintiffs' success."); *Polaroid Corp. v. Eastman Kodak Co.*, 641 F. Supp. 828, 832-33 (D. Mass. 1985) ("The evidence presented is, however, inadequate to permit me to assign to any one patent credit for the commercial success of the whole. Accordingly, this factor has played no part in the decision.").

86. If multiple patents cover a product and if a court is unable to determine which patent can be credited for the commercial success of the product, nexus is not established. *Am. Std., Inc*., 244 F. Supp. 2d at 996; *Polaroid,* 641 F. Supp. at 833; *see also McNeil-PPC, Inc. v. Perrigo Co*., 516 F. Supp. 2d 238, 254-55 (S.D.N.Y. 2007) (finding it "difficult to attribute whatever commercial success Pepcid Complete may enjoy to any one of the three patents" that covered the product).

87. The sales and profits of Viagra® cannot be attributed to only the '012 patent, which covers a use of sildenafil, because the compound sildenafil and its chemical properties are claimed by an earlier-issued patent – the '534 patent. Thus, it is the '534 patent, not the '012 patent, that has a nexus, if any, to sales and profits of Viagra®.

iii. No Nexus Exists Because The Asserted Secondary Considerations Are Not Attributable To Any Unique Subject Matter Of The Asserted Claims

88. Secondary considerations are relevant only if there is proof that the secondary consideration directly results from the unique characteristics of the claimed invention as opposed to other factors unrelated to the quality of the patented subject matter. *Huang*, 100 F.3d at 140; *see also King Pharm.*, 616 F.3d at 1280-81 ("King has not shown any nexus between the drug's alleged commercial success and the specific invention claimed"); *DBC*, 545 F.3d at 1384 ("the evidence does not reveal in any way that the driving force behind those sales [of the nutraceutical at issue] was the claimed combination of mangosteen fruit, mangosteen rind extract, and fruit or

vegetable juice."); *Ormco*, 463 F.3d at 1311-12 ("if the feature that creates the commercial success was known in the prior art, the success is not pertinent"). *See also B.E. Meyers & Co.*, 47 Fed. Cl. at 378-79 (finding that "[d]espite this definitional elasticity, plaintiff fails to provide any specific examples of a direct connection between its know-how, improvements, and manufacturing processes, and the claimed features of its invention as embodied in the language of the particular patent claims it alleges were infringed").

89. Sildenafil is not a unique feature of claims 25 and 26 of the '012 patent because, as explained above, sildenafil was known in the prior art as a PDE inhibitor. Oral administration for treating ED is similarly not unique because it was known in the prior art that ED could be treated by oral administration of compounds.

90. Although oral administration is a limitation of claims 25 and 26 of the '012 patent, further proof that the oral treatment of ED is not the alleged invention covered by those claims, and therefore not a unique feature of those claims, is that Pfizer has not been able to use the '012 patent to prevent others from marketing non-sildenafil PDE5 inhibitors for oral administration for the treatment of ED. Pfizer's inability to halt the sales of non-sildenafil PDE-5 inhibitors despite its overwhelming economic incentive to do so, and the substantial sales obtained by those competing products, demonstrate that claims 25 and 26 of the '012 patent are not responsible for Viagra's® sales and profits, and that oral administration is not a unique feature of those claims. Consequently, there is no nexus between the sales of Viagra®, or any other secondary consideration of non-obviousness, and claims 25 and 26 of the '012 patent.

91. Market outcomes arising from the profit-maximizing actions of firms are important indications of the relative market position of competing products and a better indicator

of whether there is a nexus between the sales and profits of a particular product or method and a particular patent than a prior statement about the scope of the claims.

92. Market outcomes for the competing PDE5 inhibitors administered to treat ED and Pfizer's inability to halt the substantial sales of non-sildenafil PDE5 inhibitors administered orally to treat of ED, demonstrate that there is no nexus between the sales and profits of Viagra® and claims 25 and 26 of the '012 patent, which cover the oral administration of the PDE5 inhibitor sildenafil to treat ED.

iv. The Sales And Profits Of Viagra® At The Time Of Launch Were Due, In Part, To Pfizer's Aggressive Marketing And Advertising Near The Time Of Launch

93. "[A] massive marketing and advertising campaign in connection with" the product at issue "obscur[es] any nexus that might have existed between the merits of the product and its commercial success." *See McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003); *see also Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 316 (Fed. Cir. 1985) (holding that a patentee failed to show required nexus where the sales/market share may have been attributable to extensive marketing and patentee's position as a market leader before the introduction of the patented product).

94. If the alleged success could just as easily be attributed to marketing power or capabilities, even if the Court finds that the claimed invention was a "commercial success," that evidence should not overcome a *prima facie* showing of obviousness. *Brown & Williamson*, 229 F.3d at 1129-30 (relying in part on marketing efforts that led to alleged commercial success of patented product to find that there was sufficient evidence to rebut any alleged nexus between the invention and the commercial success).

95. The Federal Circuit has found that aggressive and effective marketing tactics can undercut any alleged nexus between the patent and the alleged commercial success of the

product. *DBC*, 545 F.3d at 1384 (finding that the alleged success of the commercial product was in part due to aggressive and effective marketing).

96. The sales that Viagra® obtained at the time of its U.S. launch were due to numerous factors that were unrelated to claim 25 or 26 of the '012 patent, including pre-launch publicity cultivated by Pfizer, high levels of promotion at the time of launch and an aggressive distribution plan that reduced by 75% the typical time needed to obtain nationwide distribution. Pfizer's aggressive marketing and advertising near the time of launch undercuts any alleged nexus between the sales of Viagra® and claims 25 and 26 of the '012 patent.

(b) Viagra® Does Not Meet Any Long-Felt Need

97. "Evidence that an invention satisfied a long-felt and unmet need that existed on the patent's filing date is a secondary consideration of non-obviousness." *See Perfect Web Techs. v. Info. USA, Inc.*, 587 F.3d 1324, 1332 (Fed. Cir. 2009).

98. Mere argument that a need existed and was met is not sufficient to rebut a *prima facie* case of obviousness. Rather, the patentee must show evidence that a need actually existed and was actually met. *See Perfect Web Techs*., 587 F.3d at 1332-33 (no long felt need without evidence or data showing that the invention satisfied any long-felt need); *Amazon.com, Inc. v. Barnsandnoble.com, Inc*., 239 F.3d 1343, 1366 (Fed. Cir. 2001) (patentee could not rebut obviousness case when it presented no evidence that the invention solved a long-felt need); *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 1575 (Fed. Cir. 1983) (no long-felt need when the industry did not recognize the invention as fulfilling such a need); *In re Cavanagh*, 436 F.2d 491, 496 (C.C.P.A. 1971) (rejecting patentee's argument that its invention satisfied a long-felt need "because they are only arguments, unsupported by evidence").

99. The fact that the alleged invention was not necessarily practiced before the filing date of the asserted patent does not mean that a long-felt need existed. *Iron Grip Barbell Co.,*

Inc. v. USA Sports, Inc., 392 F.3d 1317, 1325 (Fed. Cir. 2004) ("mere passage of time without the claimed invention is not evidence of nonobviousness" absent a showing of long-felt need or the failure of others); *In re Nettel*, 972 F.2d 1354, 1992 WL 124285, at * 3 (Fed. Cir. 1992) ("Just because an invention did not exist before does not necessarily mean that there was a need that was long felt.").

100. The long-felt need must not have been satisfied by the prior art. *Newell*, 864 F.2d at 768 ("[O]nce another supplied the key element, there was no long-felt need or, indeed, a problem to be solved … ."); U.S. Pat. & Trademark Office, U.S. Dep't of Commerce Manual of Patent Examining Procedure § 716.04 (8th ed., 8th rev. 2010).

101. According to Supreme Court and Federal Circuit precedent, prior art does not have to be commercialized to satisfy a long-felt need before the subject matter of the asserted claims satisfy that alleged long felt need. *Graham*, 383 U.S. at 36 ("It is also irrelevant that no one apparently chose to avail himself of knowledge stored in the Patent Office and readily available by the simple expedient of conducting a patent search – a prudent and nowadays common preliminary to well organized research."); *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1583 (Fed. Cir. 1996) (affirming a district court's finding that "[t]he assertion of 'long-felt need' was discounted because the … invention was similar to the teachings of [a prior art publication]").

102. Any satisfaction of a long-felt need must have a sufficient nexus to the subject matter of the patent rather than a nexus to features that are in the prior art or that are not claimed by the patent. *See Pentec, Inc.*, 776 F.2d at 317 ("That testimony indicates the need for disposable pens per se, not for the claimed invention."); *Asyst*, 544 F.3d at 1316 ("While the evidence shows that the overall system drew praise as a solution to a long felt need, there was no

evidence that the success of the commercial embodiment of the '421 patent was attributable to the substitution of a multiplexer for a bus…"). *See also Sjolund v. Musland*, 847 F.2d 1573, 1582 (Fed. Cir. 1988) ("Because the lattice construction of Sjolund's tanner board is not part of his claimed invention, the advantages ascribed to the lattice construction are irrelevant in terms of the obviousness analysis."); 2 Donald S. Chisum, Chisum on Patents, § 5.05[1][c] (2007) (explaining that to be probative of nonobviousness, the objective evidence must contain a nexus between what it purports to show, *i.e.*, long-felt need, and the features of the claimed invention).

103. The "lack of commercial success in marketing also negates the argument that the [asserted] patent solved a long-felt need." *Wentworth v. Gulton Indus.*, 578 F. Supp. 508, 530 n.27 (N.D. Tex. 1982). As a district court hearing another ANDA case explained recently, "[t]he Federal Circuit has long recognized the relevance of commercial success to the question of whether an 'unmet need' has been met." *Santarus*, 720 F. Supp. 2d at 456 n.21; *see also McNeil-PPC*, 516 F. Supp. 2d at 255 n.8 (S.D.N.Y. 2007) (finding no unmet need in an ANDA case for the same reasons given for rejecting a claim of commercial success).

104. The need in the art for a selective PDE5 inhibitor is legally insufficient for purposes of finding non-obviousness because claims 25 and 26 of the '012 patent do not claim the use of all PDE5 inhibitors for the oral treatment of ED. Moreover, any alleged need for a selective PDE5 inhibitor for treating ED was met by Pfizer's EP '756 and '534 patents, which existed in the prior art.

105. By June 1993, a POSA would have understood how to use a selective PDE5 inhibitor to treat ED, and would have known that sildenafil is a selective PDE5 inhibitor. A POSA, however, would not have had access to sildenafil. The reason that there was no effective oral treatment for ED prior to Viagra® is that Pfizer controlled the compound, sildenafil. This

has nothing to do with the invention claimed in the '012 patent, which is a method of using sildenafil, a method that, as explained as part of Teva's *prima facie* case, would have been obvious to a POSA.

106. The sales and profits of Viagra® are at most only a weak indicator of the non-obviousness of claims 25 and 26 of the '012 patent and are therefore only a weak indicator of long-felt need.

107. There was no long-felt need for a method of treating ED with sildenafil in particular. To the extent that there might have been a long-felt need, it was for the oral treatment of ED generally, which is not covered by claims 25 and 26 of the '012 patent. Consequently, there is no nexus between the alleged satisfaction of a long-felt need by Viagra® and claims 25 and 26 of the '012 patent.

(c) There Is No Evidence Of "Unexpected Results"

108. Once a *prima facie* showing of obviousness has been made, the burden shifts to the plaintiff to demonstrate that its claimed invention possesses an unexpected property over the prior art. *See In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997). An applicant may make that showing "with evidence that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would find surprising or unexpected." *Id.* "It is well settled that unexpected results must be established by factual evidence." *In re Youngblood*, 1999 WL 504243, at *7 (Fed. Cir. 1999) (internal quotations omitted).

109. An unexpected property is a significantly superior property or advantage of an invention that a person of ordinary skill in the art would have found surprising or unexpected in light of the prior art. *In re Merck & Co.*, 800 F.2d 1091, 1098-99 (Fed. Cir. 1986). Unexpected results must be "different in kind and not merely in degree from the results of the prior art." *Huang*, 100 F.3d at 139.

110. "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). *See also Pfizer*, 480 F.3d at 1370-71; *Merck & Co.*, 800 F.2d at 1098-99. *See, e.g., E.I. DuPont De Nemours & Co. v. Monsanto Co.*, 903 F. Supp. 680, 766 (D. Del. 1995); *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984) (finding that appellants' assertions of unexpected results could not establish patentability due, in part, to the "absence of tests comparing appellants' heat shrinkable articles with those of the closest prior art").

111. "[B]y definition, any superior property must be *unexpected* to be considered as evidence of non-obviousness. Thus, in order to properly evaluate whether a superior property was unexpected, the court [must consider] what properties were expected." *Pfizer*, 480 F.3d at 1371. The fact that one compound is more active than another and that the exact magnitude of the difference could not be predicted by a POSA does not preclude a conclusion of obviousness. *Longi*, 759 F.2d at 897 ("There is nothing to show that the results … were unexpected. The fact that some titanium compounds function more effectively, and that the exact magnitude of the increased catalytic activity might not be predictable, does not preclude a conclusion of obviousness. Only a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness."); *see Merck & Co.*, 800 F.2d at 1098-99 (confirming the Board's finding that the properties and effects of the claimed invention were not "significantly or unexpectedly different from the level of those properties exerted by the closest prior art" because, although there were some differences in test results, the claimed invention and the closest prior art "expectedly have the same type of biological activity") (internal quotations omitted).

112. For a claimed invention to have "unexpected results," there must be a nexus between the evidence of the unexpected properties and the claimed invention. *See, e.g., Ex parte Jella*, App. No. 2008-1619, 90 U.S.P.Q. 2d 1009, 1017 (B.P.A.I. Nov. 3, 2008); *Muniauction*, 532 F.3d at 1327-28.

113. Evidence of unexpected results will not necessarily overcome a strong *prima facie* showing of obviousness. *See Pfizer*, 480 F.3d at 1372 (concluding that the record establishes such a strong case of obviousness that Pfizer's alleged unexpectedly superior results are ultimately insufficient to rebut); *Richardson-Vicks*, 122 F.3d at 1484 (holding that the "unexpected results and commercial success of the claimed invention, although supported by substantial evidence, do not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious").

114. There is no evidence of a nexus between the invention claimed in claims 25 and 26 of the '012 patent and to any alleged unexpected results. Sildenafil and its chemical properties are claimed in the '534 patent, which was in the prior art. Therefore, if there are any unexpected results, they are attributable to the '534 patent, not claims 25 and 26 of the '012 patent.

(d) Evidence Of "Copying" Is Not Relevant

115. The Federal Circuit and numerous district courts have held that evidence of copying by a generic pharmaceutical company is insufficient proof of non-obviousness because the Hatch-Waxman Act encourages generic pharmaceutical companies to copy branded drugs. *Purdue Pharma Prods. v. Par Pharm., Inc*., 377 Fed. Appx. 978, 983 (Fed. Cir. 2010) ("[W]e do not find compelling Purdue's evidence of copying in the ANDA context where a showing of bioequivalency is required for FDA approval."); *Santarus*, 720 F.Supp.2d at 458 (holding that reverse engineering of patented drug is not persuasive evidence of non-obviousness because "a

showing of copying is not compelling evidence of non-obviousness in Hatch-Waxman cases due to the nature of the ANDA process"); *Purdue Pharma Prods. v. Par Pharm., Inc*., 642 F.Supp.2d 329, 373-74 (D. Del. 2009) ("[A] showing of copying … is not compelling evidence of non-obviousness in the Hatch-Waxman context."); *Aventis Pharma Deutschland GmbH v. Lupin Ltd*., No. 05-421, 2006 WL 2008962, at *45 (E.D. Va. July 17, 2006), *rev'd on other grounds*, 499 F.3d 1293 (Fed. Cir. 2007) (holding that "[plaintiff's] copying argument is weak" because the ANDA process allows a generic drug company to challenge a drug patent by alleging the patent is invalid and because there is a statute in place that encourages generic drug companies to challenge patents).

116. The Hatch-Waxman Act provisions for generic pharmaceuticals require that an ANDA filer demonstrate, among other things, that its proposed generic product contains the same active pharmaceutical ingredient(s) ("API") in the same specified amounts as the brand pharmaceutical. *See* 21 U.S.C. § 355(j)(2)(A). The Hatch-Waxman Act provisions also require that the generic product's API be "bioequivalent" to the already approved drug. *See* 21 U.S.C. § 355(j)(2)(A)(iv). A generic product is bioequivalent if the extent and rate of absorption of the API are not significantly different from that of the already approved drug. *See* 21 U.S.C. § 355(j)(8)(B)(i).

117. Moreover, to obtain FDA approval, the law requires Teva to mirror the Viagra® label in virtually every respect. *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 15 U.S.C. §§ 68b-68c, 70b (1994); 21 U.S.C. §§ 301 note, 355, 360cc (1994); 28 U.S.C. § 2201 (1994); 35 U.S.C. §§ 156, 271, 282 (1994)). Teva's use of the same language in its proposed generic label as the language used in the brand label therefore is not evidence of copying and does not support a showing of

nonobviousness. Any argument that copying by a generic pharmaceutical company evidences non-obviousness is weak. *See Purdue Pharma Prods*., 377 Fed. Appx. at 983; *Santarus*, 720 F.Supp.2d at 458; *Aventis*, 2006 WL 2008962, at *45; *Purdue Pharma*, 642 F.Supp.2d at 373-74 (D. Del. 2009).

118. The Federal Circuit has explained that even outside of the Hatch-Waxman context, a showing of copying has limited probative value. *Geo M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (noting "that a showing of copying is only equivocal evidence of non-obviousness"); *Friskit Inc. v. RealNetworks Inc*., 306 Fed. Appx. 610, 617 (Fed. Cir. 2009) (noting that copying has limited probative value absent evidence of failed development efforts by the accused or of more compelling secondary considerations).

119. The Federal Circuit has held that "more than the mere fact of copying by an accused infringer is needed to make that action significant to a determination of the obviousness issue." *Cable Electric Prods., Inc. v. Genmark, Inc*., 770 F.2d 1015, 1028 (Fed. Cir. 1985), *overruled on other grounds by, Midwest Indus., Inc. v Karavan Trailers, Inc.*, 175 F.3d 1356 (Fed. Cir. 1999); *see also Vandenberg v. Dairy Equip. Co*., 740 F.2d 1560, 1567-68 (Fed. Cir. 1984) (finding that evidence of actual copying was "not strong evidence of nonobviousness"). The Plaintiff must offer evidence to "establish that there was a nexus between these claims and the merits" of the invention of the patent in suit for copying to possibly support a finding of nonobviousness. *Imperial Chem. Indus. v. Danbury Pharmacal, Inc*., 777 F. Supp. 330, 373 (D. Del. 1991) (finding no evidence of copying and no evidence of a nexus between copying claims and the merits of the patented invention); *see also Amazon.com, Inc.*, 239 F.3d at 1366 (Fed. Cir. 2001) ("[E]vidence of copying Amazon's '1-click®' feature is legally irrelevant unless the '1-click®' feature is shown to be an embodiment of the claims."); *Cable Electric*, 770 F.2d at 1028

(patentee must present evidence of a "'nexus' between any copying arguably shown and the nonobviousness of the claimed invention").

120. Any alleged evidence of a nexus that Plaintiffs presents must "detail what aspect(s) of the invention claimed in the [patent] was (were) targeted by industry copyists." *GPAC*, 57 F.3d at 1580; *see also Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 631 F.Supp.2d 1010, 1038-39 (N.D. Ill. 2009) ("Wrigley has not offered evidence suggesting that the novel combination of WS-23 and menthol is what led Cadbury to copy Wrigley's chewing gums, and in the absence of such evidence the Court cannot find a nexus between Cadbury's copying and the merits of the claimed invention.").

121. Although "copying by a competitor may be a relevant consideration in the secondary factor analysis … [n]ot every competing product that arguably falls within the scope of a patent is evidence of copying." *Iron Grip*, 392 F.3d at 1325; *see also Wyers*, 616 F.3d at 1246; *Cable Electric*, 770 F.2d at 1028 ("It is simplistic to assert that copying per se should bolster the validity of a patent.").

122. The fact that generic companies such as Teva are seeking FDA approval to market a generic version of Viagra® is insufficient to overcome Teva's *prima facie* showing of obviousness in light of the Hatch-Waxman requirements.

123. Copying portions of a specification is different than copying an "invention."

124. There is no nexus between any alleged copying of Viagra® and Claims 25 and 26 of the '012 patent because competitors of Pfizer developed PDE5 inhibitors whose use for the treatment of ED is not covered by those claims.

(e) Plaintiffs' Evidence Of Praise Is Insufficient

125. To be considered objective indicia of nonobviousness, evidence of praise must have a nexus to the claimed subject matter of the patent-in-suit. *See Geo M. Martin Co.*, 618

F.3d at 1305 ("Industry praise must also be linked to the patented invention."); *Muniauction*, 532 F.3d at 1328; *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1365 (Fed. Cir. 2007) ("The problem with that evidence is that there was no indication that the praise for the inventors' work was based on any inventive contribution they made, as opposed to their proof, through laboratory work, that fetal blood contains large numbers of stem cells. As noted, the former is a basis for patentability; the latter is not.").

126. There is no evidence of a nexus between any alleged praise in the industry for Viagra® and claims 25 and 26 of the '012 patent.

(f) Plaintiffs' Evidence Of Skepticism Or Surprise Is Insufficient

127. To be properly considered objective indicia of nonobviousness, evidence of skepticism or surprise must have a nexus to the claimed subject matter of the patent-in-suit. *See Muniauction*, 532 F.3d at 1328; *Pharmastem*, 491 F.3d at 1365. Evidence of surprise that is "tied" to work or research on the claimed invention that took place after the filing of the relevant patent application lacks relevance. *Pharmastem*, 491 F.3d at 1365 ("Dr. Bernstein tied the 'surprise' of his research group to the success of the 1988 human cord blood transplant, not to the results reported in the patents. Although the transplant was based on work done by the inventors, it took place long after the filing of the application for the '681 patent and shortly before the filing of the application for the '553 patent. As a result, the specification of the '681 patent does not refer to the 1988 transplant at all, and the specification of the '553 patent does not contain any account of the results of that transplant.").

128. A POSA would not have been surprised by, or skeptical about, the results of the subject matter claimed in claims 25 and 26 of the '012 patent – a POSA would have reasonably expected that the compounds recited for use in the method of claims 25 and 26 of the '012 patent could be administered orally to treat ED.

129. Evidence regarding whether a POSA would have expected an oral ED treatment to actually work, and whether potential systemic effects taught away from oral treatments for ED, does not impact the analysis of the obviousness of claims 25 and 26 of the '012 patent because that evidence relates to oral ED treatments generally rather than to the specific subject matter in claims 25 and 26.

130. Claims 25 and 26 of the '012 patent do not contain any element that relates to side effects, including side effects caused by oral/systemic administration of the compounds for use in the claimed method.

(g) Plaintiffs' Evidence Of Failures Of Others Is Insufficient To Rebut Teva's Strong Prima Facie Case of Obviousness

131. Evidence of the "failure of others to achieve the results of the invention" is an example of a secondary consideration. *Scimed Life Sys., Inc. v. Johnson & Johnson*, 225 F. Supp. 2d 422, 440 (D. Del. 2002).

132. To be properly considered objective indicia of nonobviousness, evidence of failures of others must have a nexus to the claimed subject matter of the patent-in-suit. *See, e.g.*, *Geo M. Martin Co.*, 618 F.3d at 1305 (finding evidence of failure of others insufficient to prove nonobviousness); *DyStar*, 464 F.3d at 1371-72; *see also Muniauction*, 532 F.3d at 1327.

133. Evidence of failure of others must show that others in fact tried and failed. *DyStar*, 464 F.3d at 1371-72 (finding no failure because "Buffalo's decision was [] not a failed attempt, but a calculated business judgment to abandon a potential new product line"); *see also Boston Scientific Scimed Inc. v. Cordis Corp.*, 554 F.3d 982, 991-92 (Fed. Cir. 2009) (finding the failure to be something other than a failure to conceive of a claimed feature).

134. Pfizer's exclusive control of the '534 patent, which claims sildenafil, effectively blocked others from developing sildenafil and the other eight compounds in claims 25 and 26 of the '012 patent for the oral treatment of ED.

4. Conclusion

135. For the reasons stated above, the court should give little weight to each and all of Pfizer's alleged secondary considerations. In light of Teva's strong *prima facie* showing that claims 25 and 26 of the '012 patent are obvious, the Court should find that any and all of Pfizer's asserted secondary considerations are insufficient to rebut Teva's showing of non-obviousness.

VI. CLAIMS 25 AND 26 OF THE '012 PATENT ARE INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

A. Obviousness-Type Double Patenting

136. The doctrine of double patenting seeks to "prevent a patentee from obtaining a time-wise extension of [a] patent for the same invention or an obvious modification thereof." *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d 1371, 1375 (Fed. Cir. 2008). The predecessor court to the Federal Circuit has explained the reason behind that doctrine:

> The public should … be able to act on the assumption that upon the expiration of the patent it will be free to use not only the invention claimed in the patent but also modifications or variants which would have been obvious to those of ordinary skill in the art at the time the invention was made, taking into account the skill in the art and prior art other than the invention claimed in the issued patent.

In re Zickendraht, 319 F.2d 225, 232 (CCPA 1963) (Rich, J., concurring).

137. There are two forms of double patenting: (1) statutory double patenting under 35 U.S.C. § 101 which prohibits a later patent from covering the subject matter identical to that which as claimed in an earlier patent, and (2) non-statutory judicially created obviousness-type double patenting, which prevents a later patent from covering an obvious variation of an earlier

patented invention. *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1372-73 (Fed. Cir. 2005); *see Geneva Pharms., Inc. v. Glaxosmithkline PLC*, 349 F.3d 1373, 1377-78 (Fed. Cir. 2003). This case concerns non-statutory or obviousness-type double patenting.

138. Obviousness-type double patenting prohibits "claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent." *In re Basell*, 547 F.3d at 1375; *see also Georgia-Pacific Corp. v. U.S. Gypsum Co.*, 195 F. 3d 1322, 1326 (Fed. Cir. 1999) ("Obviousness-type double patenting is a judicially created doctrine grounded in public policy, which prevents the extension of the term of the original patent via the patenting of an obvious variation.").

139. An obviousness-type double patenting analysis consists of two steps. *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 518 F.3d 1353, 1363 (Fed Cir. 2008). First, "'a court construes the claim[s] in the earlier patent and the claim[s] in the later patent and determines the differences.'" *Id.* (quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001)). Second, the court "determines whether those differences render the claims patentably distinct." *Id.* "A later patent claim that is not patentably distinct from" an earlier claim is invalid for obviousness-type double patenting. *Id. See, e.g., In re Berg*, 140 F.3d 1428, 1431-32 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 1052 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887 (Fed. Cir. 1985).

140. The first step of the obviousness-type double patenting inquiry is different from a regular obviousness inquiry in that the requisite starting point for the obviousness-type double patenting inquiry is the subject matter covered by the claims of the patents. In contrast, a regular obviousness inquiry, the Court compares the patent claims to the prior art.

141. In construing the claims of the two patents in an obviousness-type double patenting inquiry, the Court can consult the specification to ascertain the scope and meaning of

the claim. *Sun Pharm. Indus. Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1387-88 (Fed. Cir. 2010); *Vogel*, 422 F.2d at 442 (explaining that the disclosure may be used to understand whether the claimed embodiment has been modified in an obvious manner).

142. The second step in a double patenting analysis is to determine whether the claims in the patent at issue cover an invention that is patentably distinct from the claimed invention of the earlier commonly owned patent. *See Lilly*, 251 F.3d at 968. As part of that analysis, the Court can consider the conventional wisdom, *i.e.*, what was commonly known to a POSA, as well as specific prior art references. *Longi*, 759 F.2d at 893, 896; *Braithwaite*, 379 F.2d at 600; *Bayer AG v. Dr. Reddy's Laboratories, Ltd.*, 518 F. Supp. 2d 617, 641-42 (D. Del. 2007).

143. "In general, the obviousness analysis applies to double patenting, except for three distinctions. First, statutory obviousness compares claimed subject matter to the prior art, while non-statutory double patenting compares claims in an earlier patent to claims in a later patent or application. Second, double patenting does not require inquiry into a motivation to modify the prior art. Finally, double patenting does not require inquiry into objective criteria suggesting non-obviousness." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 999 (Fed. Cir. 2009).

144. In assessing obviousness-type double patenting, courts generally apply a "one-way" test. *Eli Lilly*, 251 F.3d at 968; *see also Berg*, 140 F.3d at 1432. Under a one-way test, the court asks whether the claims of a later issued patent are obvious over the claims of a commonly owned, earlier issued patent. *Eli Lilly*, 251 F.3d at 968; *see also Berg*, 140 F.3d at 1432. In some situations, however, courts apply a "two-way" test, under which the court also ask whether the earlier issued claims are obvious over the later issued claims. *Berg*, 140 F.3d at 1432; *see also In re Braat*, 927 F.2d 589, 593 (Fed. Cir. 1991). The Federal Circuit has said that a two-

way test is only appropriate when: (1) the claims at issue are in the earlier filed application; (2) applicant could not have filed the claims in a single application; and (3) "in the unusual circumstance that the PTO is solely responsible for the delay in causing the second-filed application to issue prior to the first." *Berg*, 140 F. 3d at 1437 (emphasis added); *Eli Lilly*, 251 F.3d at 968 n.7. The two-way test is considered a "narrow exception" to the general rule that the one-way test applies to obviousness-type double patenting. *Berg*, 140 F.3d at 1432.

B. **Claims 25 And 26 Of The '012 Patent Are Invalid For Obviousness-Type Double Patenting Over Claim 1 Of The '270 Patent In View Of The General Knowledge Of A POSA, As Evidenced By WO '104, EP '756 And EP '004**

145. The '270 patent qualifies as a double patenting reference against claims 25 and 26 of the '012 patent. *Brigham & Women's Hospital Inc. v. Teva Pharaceuticals USA, Inc.*, 761 F. Supp. 2d 210, 225 n. 17 (D. Del. 2011).

146. A one-way test is appropriate for analyzing whether claims 25 and 26 of the '012 patent are invalid for obviousness-type double patenting over claim 1 of the '270 patent. The conditions necessary to warrant a two-way test are not present.

147. Claim 25 of the '012 patent is not patentably distinct from claim 1 of the '270 patent in view of the general knowledge of a POSA, as evidenced by WO '104, EP '756 and EP '004.

148. Claim 26 of the '012 patent is not patentably distinct from claim 1 of the '270 patent in view of the general knowledge of a POSA, as evidenced by WO '104, EP '756 and EP '004.

149. Claim 25 of the '012 patent is invalid for obviousness-type double patenting over claim 1 of the '270 patent.

150. Claim 26 of the '012 patent is invalid for obviousness-type double patenting over claim 1 of the '270 patent.

Dated: July 5, 2011

Respectfully submitted,

/s/

Gregory N. Stillman (VSB #14308)
HUNTON & WILLIAMS LLP
500 East Main Street, Suite 1000
Norfolk, VA 23510
Telephone: (757) 640-5300
Facsimile: (757) 625-7720
gstillman@hunton.com
Counsel for Defendant and Counterclaim Plaintiff Teva Pharmaceuticals USA, Inc.

Brent L. VanNorman (VSB #45956)
HUNTON & WILLIAMS LLP
500 East Main Street, Suite 1000
Norfolk, VA 23510
Telephone: (757) 640-5300
Facsimile: (757) 625-7720
bvannorman@hunton.com
Counsel for Defendant and Counterclaim Plaintiff Teva Pharmaceuticals USA, Inc.

Kevin J. Culligan (admitted *pro hac vice*)
David M. Hashmall (admitted *pro hac vice*)
John P. Hanish (admitted *pro hac vice*)
Keith A. Zullow (admitted *pro hac vice*)
Joshua A. Whitehill (admitted *pro hac vice*)
Charles Wizenfeld (admitted *pro hac vice*)
GOODWIN PROCTER LLP
The New York Times Building
620 Eighth Avenue
New York, NY 10018-1405
Telephone: (212) 813-8800
Facsimile: (212) 355-3333
kculligan@goodwinprocter.com
dhashmall@goodwinprocter.com
jhanish@goodwinprocter.com
kzullow@goodwinprocter.com
jwhitehill@goodwinprocter.com
cwizenfeld@goodwinprocter.com
Counsel for Defendant and Counterclaim Plaintiff Teva Pharmaceuticals USA, Inc.

CERTIFICATE OF SERVICE

I hereby certify that on the 5th day of July, 2011, I will electronically file the foregoing Teva's Post-Trial Findings of Fact and Conclusions of Law On Standing and Validity with the Clerk of Court using the CM/ECF system, which will then send a notification of such filing to the following counsel of record:

Conrad M. Shumadine (VSB #4325)
Email: cshumadine@wilsav.com
Brett A. Spain (VSB #44567)
Email: bspain@wilsav.com
WILLCOX & SAVAGE
440 Monticello Avenue, Suite 2200
Norfolk, VA 23510
Telephone: (757) 628-5500
Facsimile: (757) 628-5566

Coke Morgan Stewart (VSB #41933)
Email: coke.stewart@kayescholer.com
R. William Sigler (VSB #65940)
Email: bill.sigler@kayescholer.com
KAYE SCHOLER LLP
The McPherson Building
901 Fifteenth Street, NW
Washington, DC 20005
Telephone: (202) 682-3500
Facsimile: (202) 682-3580

Aaron Stiefel *(admitted pro hac vice)*
Email: astiefel@kayescholer.com
Daniel P. DiNapoli *(admitted pro hac vice)*
Email: ddinapoli@kayescholer.com
Marc N. Zubick *(admitted pro hac vice)*
Email: mzubick@kayescholer.com
Soumitra Deka *(admitted pro hac vice)*
Email: sdeka@kayescholer.com
KAYE SCHOLER LLP
425 Park Avenue
New York, NY 10022
Telephone: (212) 836-8000
Facsimile: (212) 836-8689

Alan Michael Fisch (*admitted pro hac vice*)
Email: alan.fisch@kayescholer.com
KAYE SCHOLER LLP
The McPherson Building
901 Fifteenth Street, NW
Washington, DC 20005
Telephone: (202) 682-3500
Facsimile: (202) 682-3580

Counsel for Plaintiffs and Counterclaim Defendants Pfizer Inc., Pfizer Limited, Pfizer Ireland Pharmaceuticals (a Partnership) and Pfizer Ireland Pharmaceuticals (an Unlimited Liability Company)

/s/
Gregory N. Stillman (VSB #14308)
HUNTON & WILLIAMS LLP
500 East Main Street, Suite 1000
Norfolk, VA 23510
Telephone: (757) 640-5314
Facsimile: (757) 625-7720
gstillman@hunton.com

Counsel for Defendant and Counterclaim Plaintiff Teva Pharmaceuticals USA, Inc.